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SOBEE

is a soy bean preparation free from milk protein, indicated in eczema from protein sensitization or other forms of milk idiosyncrasy.

The principal difficulty in the dietary treatment of these cases lies in the fact that milk-free diets, upon the withdrawal of protein, result in metabolic imbalance and often serious sequelae. Blackfan says, "In infants this form of treatment is unsafe when continued for a long time, because a non-protein diet cannot be substituted for cow's milk and human milk without incurring the risk of a severe nutritional disturbance."

Schloss states, "It is obvious that definite proof of the allergic nature of infantile eczema must depend on the development of a food free from milk protein, which is capable of maintaining nutrition." With this in view, research was undertaken by Hill and Stuart to develop a food containing protein in sufficient quantities to maintain nutrition and insure normal growth even with long-continued use, to be used in cases where milk protein is the offending factor. A soy bean preparation with the requisites of adequate caloric and nutritional value, ease of tolerance and clinical success has resulted.

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Leading medical authorities now agree that the proteins of milk, cereals, and eggs are responsible for most of the allergies of infancy. But until recently it has been virtually impossible to withdraw these offending proteins, for lack of a substitute containing other proteins of a kind and quantity adequate to maintain normal growth. Now in Sobee and in Cemac the physician has his choice of two such foods, either of which can be administered as the exclusive diet for infants.

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A Diet Free from Animal Protein

Sobee is a soybean product consisting of 61.0% refined soybean flour, 19% olive oil, 9% arrowroot starch, 6% Dextri-Maltose, 4% dicalcium phosphate, and 1% sodium chloride. When Sobee is reliquefied with water and Dextri-Maltose No. 2 is added, the analysis in many respects approximates that of the usual cow's milk formula. Supplemented with cod liver oil and orange juice, it will maintain infants over an extended period as the sole source of food. The flavor of Sobee has recently been improved, so that infants take the mixture readily and gain normally. Levy and Finkelstein[1] state that 38 of 40 infants sensitive to milk proteins showed definite improvement when placed on a Sobee diet. Klein,[2] Rowe,[3] Clarke,[4] and others report equally good results. Hill, describing the treatment of 80 eczematous infants with Sobee, observes that results were remarkable in some instances, severe eczema disappearing within a few days.

Supplied in 1 and 4 lb. tins.

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Many children are sensitive not only to milk proteins but to those of eggs and cereals as well. If the allergic infant is placed on a diet of Cemac, any or all of these proteins can be withdrawn without danger. A mixture of beef, cauliflower, tomatoes, carrots, spinach, cane sugar, Dextri-Maltose, olive oil, cod liver oil, dicalcium phosphate, and sodium acid phosphate, Cemac is designed to supply all the nutritive requirements, including vitamins C and D, for normal growth of infants. Cooked, strained, and homogenized, Cemac is ready for immediate use after dilution with boiled water. It may be fed from the nursing bottle or as a soup. Like Sobee, its analysis is similar to that of the usual milk formula.

Since 1925 Cohen and his associates[5] at the Asthma, Hay Fever, and Allergy Foundation, Cleveland, have been feeding allergic children on this vegetable soup. "Allergic infants," Cohen reports, "thrive on this diet. In the vast majority the allergic symptoms disappear."

Supplied in 1 lb. tins.

[1-5] *Bibliography on request.*

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The Journal of Allergy

VOL. IV SEPTEMBER, 1933 No. 6

Original Articles

THE ALLERGEN CONTENT OF POLLEN EXTRACTS. ITS DETERMINATION AND ITS DETERIORATION*†

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JEAN TENNANT, M.A.
NEW YORK, N. Y.

PREVIOUS work[1-6] has indicated the protein nature of the hay fever producing allergen in ragweed, timothy, and certain grass pollens. The methods used in separating the active material were those favorable for the isolation of protein, namely, precipitation with high salt concentrations. The concentrated protein solutions gave characteristic chemical and physical tests for protein. They gave positive skin reactions in high dilutions in all the clinically sensitive cases, and they readily desensitized active serums. The protein solutions were reduced in activity by heating and alcoholic precipitation. The solid material isolated from these solutions gave characteristic elementary analyses for protein. We believe the assumption of the protein nature of this active material to be best in accord with the experimental facts. There are references in the literature supporting this view.[7-20]

The references in the literature to the nonprotein nature of pollen activity are inconclusive. Grove and Coca,[21] supporting the view of the nonprotein nature of pollen activity, have based their conclusion on the failure to inactivate ragweed pollen extract by digestion and dialysis with pangestine for three to six days. Bouillene and Bouillene[17] subsequently reported the complete inactivation of ragweed extract by digestion for fifty days with pangestine. Loeb[18] similarly has shown that foxtail and orchard grass pollen extracts were inactivated by proteolytic enzymes. These results were positive findings and con-

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†Read in abstract before the Division of Medicinal Chemistry, American Chemical Society, March 28, 1933, Washington, D. C.

trary to the findings of Grove and Coca.[21] Black[22] reported an active polysaccharide precipitated by alcohol from ragweed extract containing 55 per cent reducing sugar and 6 per cent nitrogen and concluded it was an active factor. The authors[1] with Chobot had previously described a polysaccharide material precipitated by alcohol from ragweed extract. One preparation contained 60 per cent reducing sugar and 5.7 per cent nitrogen. It gave skin reactions in the more sensitive cases but not in all the clinically sensitive. It failed to desensitize serum against whole pollen extract and failed to give reactions in skin sites desensitized by the purified protein free of carbohydrate.[2] We believe the slight activity of the polysaccharide fraction was due to traces of protein as indicated by its nitrogen content.

In direct skin tests, dilutions of the purified active pollen protein[2] containing 1:10,000,000 gm. protein nitrogen per cubic centimeter gave skin reactions in moderately sensitive cases. The activity tests were much more delicate than chemical tests for protein. Northrop and Kunitz[23] have shown that solutions of pepsin and trypsin containing less than 1:1,000,000 gm. per cubic centimeter of protein nitrogen had accurately measurable enzymatic activity, although these solutions gave negative protein tests; the dry material from which the solutions were made was practically pure protein, and the positive evidence indicated the protein nature of these enzymes. Similarly the positive evidence indicated the protein nature of the hay fever producing material in pollen extract. Evidence for the nonprotein nature of pollen activity was of negative nature and was based on the failure to demonstrate pollen nitrogen in extracts showing activity and on the failure to inactivate these extracts by a limited contact with a proteolytic enzyme (pangestine).

Our conclusion that albuminous protein was the only active hay fever producing substance in pollen was based on the desensitization of active pollen sensitive serums with the specific purified pollen protein by the method of passive transfer of Prausnitz and Küstner.[24] It was the only material which completely desensitized active serums against whole pollen extract and gave the typical immediate skin reaction in all the specific pollen sensitive cases tested. The protein nitrogen content of pollen extracts has been suggested as a basis for standardization[6] with 0.00001 mg. protein nitrogen as one unit.

In this paper are presented further experimental data showing the relationship between the protein nitrogen content of pollen extracts and their clinical activity and the advantages of the protein nitrogen unit as a basis for standardization.

DETERMINATION OF PROTEIN NITROGEN

The protein nitrogen (P.N.) may be determined as previously described[6] by difference between the total nitrogen (T.N.) and nonpro-

tein nitrogen (N.P.N.) after precipitation of the protein nitrogen with 10 per cent phosphotungstic acid in hydrochloric acid solution.

Instead of filtering, providing the extracts contained sufficient protein, the precipitate could be analyzed directly for protein nitrogen by carrying out the precipitation in a centrifuge tube. An excess (about 1 c.c.) of 10 per cent phosphotungstic acid in 10 per cent hydrochloric acid solution was added to the acidified pollen extract in a centrifuge tube. After settling, the precipitate was centrifuged, and

TABLE I

COMPARISON OF METHODS FOR DETERMINATION OF PROTEIN NITROGEN IN POLLEN EXTRACTS

POLLEN EXTRACT	T. N. MG. PER C.C.		N. P. N. MG. PER C.C.		PROTEIN N., MG. PER C.C.				
					T.N.-N.P.N. (AVERAGE)	PHOSPHOTUNGSTIC ACID PPT.		ALCOHOLIC PHOSPHOTUNGSTIC ACID PPT.	
Oak	0.91	0.89	0.81	0.77	0.11			0.14	0.15
Poplar	1.25	1.25	1.04	1.05	0.20			0.16	0.17
Ash	1 37	1.39	0.84	0.83	0.54			0.51	
Plantain	0.49	0.51	0.41	0.39	0.10			0.11	0.11
Ragweed I	0.56		0.42		0.14	0.14			
Ragweed II	0.65	0.65	0.43	0.42	0.23	0.25	0.25	*(0.10	0.10)
Ragweed III	0.61	0.61	0.50	0.49	0.11			0.11	0.11
Ragweed IV	0.76		0.46		0.30	0.29			
Ragweed V	0.56		0.34	0.34	0.22	0.25	0.26		
Orchard grass	0.39		0.25		0.14	0.14			
Bermuda grass	0.37		0.19		0.18	0.17			
Red Top	0.39		0.21		0.18	0.20			
Timothy 1	0.37	0.38	0.27	0.27	0.10	0 09		0.11	0.11
Timothy 2	0.64	0.64	0.26	0.26	0.38	0.33	0.35	0.34	0.35
Timothy 2 and equal vol. of glycerin						0.17	0.18	0.15	0.16
Timothy 3 containing 50 per cent glycerin	0.27	0.27	0.17	0.15	0.11	0.13	0.13		

*_Low Result_, incomplete precipitation.

the supernatant nonprotein nitrogen was decanted. The precipitate was washed three times with a 10 per cent hydrochloric acid solution containing 0.5 per cent phosphotungstic acid, by centrifugalization and decanting the supernatant solution. Then the precipitate was dissolved in 1 per cent sodium hydroxide and transferred to a digestion flask for a Kjeldahl nitrogen determination. This gave directly the protein nitrogen content of the extract.

In certain pollen extracts, the protein nitrogen could be determined by an application of the method described by Northrop[25] for determining protein in enzyme preparations. An alcoholic phosphotungstic acid precipitating reagent[25] was used, and the precipitate was washed with the precipitating reagent by centrifugalization and was analyzed

for its nitrogen content. This method was not found applicable to all pollen extracts. In most cases, the figures were in agreement with the method by difference, but in the analysis of a certain ragweed extract, a colloidal solution resulted which failed to give complete precipitation of protein. In this instance, it was obvious that the procedure was not giving quantitative precipitation, as the supernatant fluid was not clear but deposited more precipitate over a long period.

The direct analysis of the protein precipitate was particularly useful for the analyses of glycerin extracts. The 10 per cent phosphotungstic acid in hydrochloric acid solutions gave satisfactory results in all cases. A comparison of these three methods is given in Table I.

VARIATION OF THE PROTEIN NITROGEN IN EXTRACTS OF DIFFERENT LOTS OF POLLEN

It has been shown[4] that extracts from different lots of timothy pollen when extracted under the same conditions contained varying amounts of protein nitrogen. In Table II are given the analytical results on extracts prepared from different lots of certain grass pollens. The extracts were made under identical conditions from 3 gm. of defatted pollens and 100 c.c. of alkaline-saline fluid,[6] Seitz filtered, and analyzed at the time of their preparation. Whenever pollen is

TABLE II

NITROGEN VARIATION IN EXTRACTS PREPARED FROM GRASS POLLENS
(3 gm. Pollen per 100 c.c. Alkaline Saline Fluid)

POLLEN	SEASON	DATE OF EXTRACTION AND ANALYSIS	NITROGEN, MG. PER C.C.			PERCENTAGE P.N. OF T.N.
			TOTAL	NON-PROTEIN	PROTEIN (BY DIFFERENCE)	
Bermuda *(Cyndon Capriola dactylon)*	1931	10/ 2/31	0.35	0.20	0.15	43
Red top *(Agrostis palustris)*	1931	10/ 2/31	0.37	0.22	0.15	40
Johnson *(Andropogon halepensis)*	1931	10/ 2/31	0.31	0.18	0.13	42
June	1923	3/ 1/32	0.15	0.13	0.02	13
(Poa pratensis)	1931	10/ 2/31	0.35	0.23	0.12	34
Orchard	*1922	1/10/32	0.20	0.17	0.03	15
(Dactylis glomerata)	*1931	10/ 2/31	0.35	0.22	0.13	37
Rye	1922	12/ 3/31	0.42	0.26	0.16	38
(Secale cereale)	1931	10/ 2/31	0.46	0.25	0.21	46
Timothy	*1921	6/ 1/31	0.21	0.16	0.05	24
(Phleum pratense)	*1931	6/ 1/31	0.37	0.17	0.20	54

*These extracts used for skin tests as shown in Table III.

referred to in the preparation of aqueous extracts, anhydrous ethyl ether defatted pollen was used. The extracts from these grass pollens diluted on a total nitrogen basis were not of equal activity in direct skin tests in all the grass sensitive cases, but compared favorably in

TABLE III

COMPARATIVE INTRADERMAL SKIN TESTS

		PROTEIN NITROGEN						TOTAL NITROGEN								
DIL. MG. PER C.C.		0.01			0.0001			0.01			0.001			0.0001		
EXTRACT		1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
Case	A	++++	++++	++++				+	+++	++						
	B				+	+	+							+	+++	—
	C	++++	++++	++++				++++	++++	+++						
	D				++	+++	+++				+	++++	+			
	E				++	++	++				++	+++	++			
	F				++++	++++	+++				++	+++	++			
	G				+	+	+							+	+++	—

1 = Timothy 1921 Ext.
2 = Timothy 1931 Ext.
3 = Orchard 1922 Ext.
} For analysis see Table II.
+ = Degree of skin reaction.
– = Negative skin reaction.

activity in direct test in all cases when diluted on a protein nitrogen basis. The older pollens, dark in color, gave extracts lower in protein nitrogen in proportion to the total nitrogen than extracts of new light-colored pollens. A protein nitrogen basis was superior to a total nitrogen or weight by volume basis for standardization (see Table II) since there was such a variation in extracts of different lots of pollen.

In many instances, it was impossible to determine differences in strength of extracts by direct skin tests since frequently extracts 10 and even 100 times stronger by dilution, gave identical skin reactions when readings were made within thirty minutes. Only by testing a series of cases was it possible to determine the advantage of a protein nitrogen basis over a total nitrogen basis, and then only in the case of the orchard and timothy extracts (for analyses see Table II), in which the variation in the percentage protein nitrogen approximated 30 per cent to 40 per cent. Even with these extracts in certain cases the difference was not great, but a comparison of tests on a protein and total nitrogen basis (see Table III) showed that when extracts were standardized by their protein nitrogen content they more closely agreed in direct skin test than when standardized by their total nitrogen content.

In Table IV, water extracts of different lots of ragweed are compared and the protein nitrogen varies from 24 per cent to 40 per cent of the total nitrogen. These extracts, when diluted on a protein nitrogen basis, were of equal strength when tested in a series of cases.

TABLE IV

NITROGEN VARIATION IN EXTRACTS PREPARED FROM RAGWEED POLLEN
(3 gm. Pollen per 100 c.c. of Water)

POLLEN	SEASON	DATE OF EXTRACTION AND ANALYSIS	NITROGEN (MG. PER C.C.)			PERCENTAGE P.N. OF T.N.
			TOTAL	NON-PROTEIN	PROTEIN	
Giant ragweed *(Ambrosia trifida)*	1923	Dec., 1931	0.37	0.28	0.09	24
Low ragweed *(Ambrosia artemesiaefolia)*	1923	Dec., 1931	0.30	0.18	0.12	40
Giant ragweed	1924	Dec., 1931	0.32	0.19	0.13	40
Low ragweed	1930	Dec., 1931	0.32	0.19	0.13	40
Giant ragweed	1931	Dec., 1931	0.46	0.31	0.15	33

POLLEN DETERIORATION AND ITS PREVENTION

Clinical experience and the previous analyses have shown that pollen may deteriorate. Pollens which have darkened in color or become lumpy have given extracts of poor activity and of low protein nitrogen content. A study has been made of a new timothy pollen over a period of one year (Table V). An extract of the fresh pollen was analyzed for its protein nitrogen content. At the end of a year the pollen samples, treated and preserved as shown in the table, were

again extracted and analyzed. The pollen samples were all ether defatted, dried, weighed and extracted in distilled water using 3 gm. per 100 c.c. for eighteen hours at 10° C. The results show that pollen thoroughly dried and sealed from atmospheric moisture after one year contained the original activity in terms of protein nitrogen. The atmospheric moisture was sufficient to cause deterioration. The advantage of a protein nitrogen basis over a weight by volume basis for standardization was particularly obvious in this instance.

TABLE V

PROTEIN NITROGEN CONTENT OF WATER EXTRACTS PREPARED FROM TIMOTHY POLLEN PRESERVED FOR ONE YEAR UNDER VARYING CONDITIONS

		NITROGEN IN MG. PER C.C.		
		TOTAL	NONPROTEIN	PROTEIN
1. Whole pollen open to air	Slight brown color	0.31	0.19	0.12
2. Defatted pollen open to air		0.34	0.19	0.15
*3. Whole pollen dried at 102° C. 2 hr. and sealed	Yellow color	0.40	0.19	0.21
*4. Defatted pollen dried at 102° C. 2 hr. and sealed		0.40	0.21	0.19
*5. Defatted pollen dried in vacuum over $CaCl_2$ and sealed		0.41	0.20	0.21

*Same protein content as fresh pollen.

In Table VI is given a comparison of the percentage protein nitrogen of total nitrogen in routine extracts prepared for the 1932 and 1933 seasons. It can be seen that in certain pollens the variation was considerable, as, for example, ash. This variation was probably due

TABLE VI

PERCENTAGE PROTEIN NITROGEN OF TOTAL NITROGEN IN ROUTINE EXTRACTS PREPARED FOR TWO SEASONS. ANALYSES MADE AT TIME OF PREPARATION

	PER CENT P.N. OF T.N.	
	1932	1933
Oak	20	14
Ash	18	38
Hickory I	21	30
Hickory II	38	
Poplar	14	17
Birch	23	21
Sorrel	26	38
Plantain	31	22
Timothy	50	54
Ragweed	30	34

to the deterioration in pollens. A protein nitrogen analysis of these extracts gave a means of determining the condition of the pollens. These figures indicated why in past seasons the reports of the clinical activity of pollen extracts have been so variable that in certain years new extracts were prepared to take the place of extracts of poor clini-

cal activity. It was further evidence of the advantage of the protein nitrogen as a basis for dilution that in the 1933 season, when the extracts were diluted on this basis, none were found clinically low in activity, although the percentage of protein nitrogen in plantain and oak was lower in 1933 than in 1932. In general the tree pollen extracts were lower in the percentage of protein nitrogen than timothy or ragweed.

THE PROTEIN NITROGEN CONTENT OF EXTRACTS DIFFERING IN AGE

The routine pollen extracts used in treatment in different seasons were analyzed for their protein nitrogen content (see Table VII). The variation shown may have been due to deterioration of the extract by protein hydrolysis or other factors, such as deterioration of the pollens before the extracts were prepared, and differences due to filtrations. These extracts compared better in activity by direct skin test in a series of cases when diluted on the protein nitrogen basis than when diluted by their total nitrogen. The 1916 ragweed extract compared better in skin tests with new extracts when diluted by protein nitrogen, but even then it was not as active as were new extracts.

TABLE VII

NITROGEN VARIATION IN ALKALINE SALINE POLLEN EXTRACTS DIFFERING IN AGE

POLLEN	DATE EXTRACT PREPARED	DATE OF ANALYSIS	NITROGEN (MG. PER C.C.)			PERCENTAGE P.N. OF T.N.
			TOTAL	NONPROTEIN	PROTEIN	
Giant ragweed	1916	2/ 4/32	0.77	0.68	0.09	12
	2/10/31	2/ 4/32	0.63	0.49	0.14	22
	3/ 1/32	3/ 1/32	0.63	0.46	0.17	27
Timothy	1930	2/16/32	0.32	0.24	0.08	25
	3/ 5/31	2/16/32	0.38	0.31	0.07	18
	2/16/32	2/16/32	0.40	0.20	0.20	50
Orchard	1924	3/23/32	0.34	0.29	0.05	15
	10/ 2/31	10/ 2/31	0.35	0.22	0.13	37

DETERIORATION OF POLLEN EXTRACTS OVER A ONE-YEAR PERIOD

Certain tree, grass and weed extracts prepared in alkaline-saline fluid in January and February, 1932, were analyzed for protein and total nitrogen at once and at intervals throughout a year. The extracts were preserved sterilely at 10° C. These analyses showed gradual deterioration indicated by an increase in the nonprotein nitrogen with decrease in the protein nitrogen. (See Table VIII.) The loss of active substance expressed as protein nitrogen at the end of one year approximated 50 per cent. Greater deterioration in allergic activity due to the denaturization and partial protein hydrolysis may have taken place, although not indicated by the analysis. Extracts, one or two years old, in direct skin test gave comparable reactions when diluted by their protein nitrogen. A comparative analysis of a one-

TABLE VIII

ANALYSES SHOWING LOSS OF PROTEIN NITROGEN IN POLLEN EXTRACT AFTER PERIOD OF ONE YEAR

EXTRACT	NITROGEN IN MG. PER C.C.				PERCENTAGE P. N. LOSS
	JAN., 1932		JAN., 1933		
	TOTAL	PROTEIN	TOTAL	PROTEIN	
Ragweed	0.60	0.18	0.59	0.11	39
Timothy	0.40	0.20	0.37	0.10	50
Plantain	0.44	0.14	0.42	0.06	57
Oak	0.93	0.19	0.95	0.09	53
Ash	0.59	0.11	0.59	0.06	45
Poplar	1.00	0.14	1.00	0.08	43
Birch	0.42	0.10	0.39	0.05	50
Hickory	0.41	0.09	0.34	0.03	66

year-old and a new extract has proved of value in changing the perennial cases from the old to the new extract.[26]

THE EFFECT OF ALCOHOL TREATMENT OF POLLEN ON THE PROTEIN NITROGEN CONTENT OF SUBSEQUENT EXTRACTS

Ragweed pollen rapidly washed with 85 per cent alcohol and dried with ethyl ether gave active aqueous extracts containing about one-third the nitrogen of extracts of untreated pollen, and when diluted on a weight by volume basis were not so strong in the desensitization of ragweed sensitive serums by passive transfer as aqueous extracts of the pollen not washed with alcohol. Two such ragweed extracts were analyzed and gave the results shown in Table IX.

TABLE IX

ALKALINE SALINE EXTRACTS OF RAGWEED POLLEN
3 GM. PER 100 C.C.

	NITROGEN MG. PER C.C.	
	85% alcohol washed	untreated pollen
Total	0.17	0.39
Nonprotein	0.08	0.21
Protein (by difference)	0.09	0.18

Alcoholic treatment had reduced the amount of protein and activity in subsequent aqueous extracts. It was therefore important to use anhydrous alcohol-free ether for defatting pollen.

EFFECT OF SEITZ FILTRATION ON THE ACTIVITY AND PROTEIN NITROGEN CONTENT OF EXTRACTS

The determination of the total nitrogen content of alkaline saline ragweed extract showed that Seitz filtration and various absorbents removed nitrogen. A water extract of ragweed, (P_H 6.6) was practically inactivated by treatment with norite or animal charcoal. The results are shown in Table X. Fifteen c.c. of the extracts were treated

TABLE X

RAGWEED

	ALKALINE SALINE EXTRACT (P_H 7.6) NITROGEN MG. PER C.C.	WATER EXTRACT PLUS $CACO_3$ (P_H 6.6) NITROGEN MG. PER C.C.
Total N not filtered	0.47	0.31
After Seitz filtration	0.41	
Norite and Seitz filtration	0.40	0.11 } inactive in
Animal charcoal and filtration	0.21	0.12 } skin test
Kieselguhr and filtration	0.29	0.29
Alumina gel. filtration	0.23	0.31

with 0.2 gm. of the absorbents with occasional shaking, and after two hours were Seitz filtered and all diluted the same for testing.

A routine alkaline saline extract of timothy pollen was analyzed after one Seitz filtration, and then 120 c.c. of the extract were filtered through a Seitz filter (100 c.c. capacity) a second time and analyzed.

The second filtration reduced the total nitrogen by 15 per cent and the protein, active, nitrogen by 27 per cent so that an extract twice filtered, when diluted on a total nitrogen basis, was not as high in protein nitrogen as one similarly diluted and only once filtered.

TABLE XI

TIMOTHY POLLEN EXTRACT P_H 7.6

	FIRST FILTRATION	SECOND FILTRATION
Total N mg. per c.c.	0.48	0.41
Nonprotein N mg. per c.c.	0.22	0.22
Protein N (by difference) mg. per c.c.	0.26	0.19
Protein N as per cent of total N	54	46

Clinical experience showed that certain tree pollen dilutions prepared by Seitz filtration of the higher dilutions were inactive in skin test in comparison with dilutions of the same extract prepared under sterile conditions without Seitz filtration. In Table XII are shown nitrogen determinations on dilutions which had been prepared with and without subsequent Seitz filtration. In the filtered dilutions lower nitrogen content coincided with lowered skin activity. Fifty c.c. volumes were analyzed.

TABLE XII

	NITROGEN MG. PER C.C.	
	CALCULATED BY DILUTION, NOT FILTERED	FOUND BY ANALYSIS, FILTERED DILUTION
Hickory	0.01	0.005
Plantain	0.01	0.008
Timothy	0.01	0.005
Timothy	0.05	0.04

A 0.1 mg. nitrogen per c.c. dilution of timothy pollen was prepared. It was analyzed for protein nitrogen before filtration and then after each of four successive Seitz filtrations. After the final filtration, the extract was diluted similarly to the original and comparative skin tests were made. The dilution which had been four times filtered was practically inactive.

TABLE XIII

SUCCESSIVE SEITZ FILTRATION OF A 0.1 MG. N PER C.C. DILUTION OF TIMOTHY POLLEN EXTRACT

	UNFILTERED	1 FILTRATION	2 FILTRATIONS	3 FILTRATIONS	4 FILTRATIONS
Total N mg. per c.c.	0.10	0.09	0.07	0.07	0.06
Nonprotein N mg. per c.c.	0.05	0.05	0.05		0.05
Protein N (by difference) mg. per c.c.	0.05	0.04	0.02		0.01
Protein N as per cent of total N	50	44	28		16

A STUDY OF EXTRACTION TIME

To determine whether the length of time of the extraction had any influence upon the nitrogen content and activity of the extracts, 1 gm. of ragweed pollen was extracted for varying periods at 7° C. with 33 c.c. of alkaline saline fluid. At the end of the specified time, extracts were filtered through a Seitz, duplicate nitrogens were determined on 10 c.c., and dilutions were made in buffered saline for skin testing.

TABLE XIV

TIME INTERVAL HOURS	TOTAL NITROGEN MG. PER C.C.	ACTIVITY OF DILUTIONS
3	0.39	++++
6	0.41	++++
18	0.38	++++
24	0.41	++++
72	0.40	++++

+ = Degree of skin reaction.

A short extraction period removed as much nitrogen and active protein as did longer periods.

THE EFFECT OF THE AMOUNT OF POLLEN PER UNIT VOLUME ON THE PROTEIN NITROGEN CONTENT OF THE EXTRACT

Varying weights of ragweed pollen were treated with 100 c.c. alkaline saline fluid for five hours at 7° C. with shaking every half hour. The extracts were filtered through Seitz filters and the volume adjusted to 100 c.c. by adding the necessary fluid through the filter in order to make the final volume 100 c.c. The analyses of these extracts are given below.

TABLE XV

POLLEN GM.	VOLUME C.C.	NITROGEN MG. PER C.C.			
		TOTAL	NONPROTEIN	PROTEIN	PROTEIN PER GM. OF POLLEN
1	100	0.16	0.13	0.03	0.03
3	100	0.38	0.24	0.14	0.04
9	100	0.99	0.63	0.36	0.04

The protein nitrogen was as completely extracted by 100 c.c. when nine grams of pollen were used as when one gram was used. When nine grams were used, the resulting extract had a small amount of sediment which was evidently non-nitrogenous since the extract on analysis contained the same nitrogen content after removing the sediment by the centrifuge.

PROTEIN NITROGEN CONTENT OF WATER AND ALKALINE SALINE FLUID EXTRACTS OF TIMOTHY POLLEN, SUCCESSIVE EXTRACTION

Three gm. lots of timothy pollen were extracted for five hours in 100 c.c. of water and 100 c.c. alkaline saline extracting fluid. The extracts were filtered through paper and analyzed for their total and protein nitrogen. The two pollen residues were then each extracted overnight with 50 c.c. alkaline saline fluid. The extracts were filtered similarly and analyzed for total and protein nitrogen.

TABLE XVI

WATER EXTRACTION OF TIMOTHY POLLEN. POLLEN RESIDUE SUBSEQUENTLY EXTRACTED WITH 50 C.C. ALKALINE SALINE

POLLEN	EXTRACTIVE	NITROGEN MG. PER C.C.		
		TOTAL	NONPROTEIN	PROTEIN
3 gm.	100 c.c. water	0.37	0.17	0.20
Residue	50 c.c. alkaline saline	0.15	0.06	0.09

ALKALINE SALINE EXTRACTION OF TIMOTHY POLLEN. POLLEN RESIDUE SUBSEQUENTLY EXTRACTED WITH 50 C.C. ALKALINE SALINE FLUID

POLLEN	EXTRACTIVE	NITROGEN MG. PER C.C.		
		TOTAL	NONPROTEIN	PROTEIN
3 gm.	100 c.c. alkaline saline	0.43	0.16	0.27
Residue	50 c.c. alkaline saline	0.08	0.04	0.04

The results show that in the case of timothy pollen a slightly greater amount of nitrogen was removed by the alkaline saline extracting fluid than by water. A second extraction removed only a small amount of nitrogenous protein material. Note that only half the volume of extractive was used for the second extraction.

The results showed the ready solubility of the protein material and that there was no necessity for repeated extractions over long periods of time.

SUMMARY

1. The protein nitrogen content of pollen extracts could be determined directly by analysis of the 10 per cent phosphotungstic acid protein precipitate or indirectly by the difference between the total and nonprotein nitrogen.

2. The activity of pollen extracts, as measured by the protein nitrogen content, varied according to the condition of the pollen and the age of the extract.

3. Deterioration of pollen, measured by the reduction of aqueous soluble protein, was prevented by preserving the dry pollen sealed from atmospheric conditions.

4. The loss of the protein nitrogen and activity in alkaline saline pollen extracts approximated 50 per cent at the end of one year.

5. Repeated filtration of pollen extracts reduced the activity and protein nitrogen content proportionately. The nonprotein nitrogen was not affected.

6. A study of pollen extraction has shown the ready solubility of the active protein material. Long periods of extraction or repeated extractions were not necessary for its solution.

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THE USE OF GLYCEROLATED POLLEN EXTRACTS IN THE TREATMENT OF HAY FEVER

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CLOCK[1] was the first to advocate the use of glycerin pollen extracts, in 1922. He used a solution containing 66⅔ per cent glycerin and 33⅓ per cent saturated sodium chloride solution. Since that time allergists have used varying percentages of glycerin in making up their pollen extracts.

We herewith wish to report on the use of a 50 per cent glycerolated ragweed pollen extract in a series of late hay fever cases, during the season of 1932. These extracts were supplied to me by Dr. Coca and were made by mixing strong standardized fresh extracts with an equal part of sterile glycerin.

Glycerin, or glycerol, is a colorless, viscid, sweet tasting alcohol. Its value in stabilizing solutions, especially serums, has been known for a long time.

The advantages of glycerolated pollen extracts are:

1. They are self-sterilizing; extracts made with sterile glycerin (by boiling) remain so, with the exception of spore-bearing microorganisms.

2. Extracts are stable, maintaining their full activity without deterioration for years. The tracings (Fig. 1) of skin reactions, comparing dilutions made from glycerin extracts three years old with fresh dilutions, illustrate this point, showing that the old glycerolated extracts are just as potent as the fresh saline ones, on an equal nitrogen basis.

3. At present, extracts are prepared for each season's use. Using glycerin, we can make up enough for several years' supply at one time.

4. In the perennial treatment of hay fever, now the method of choice, the advantage of using a nondeteriorating extract is apparent. In fact, it adds the last link to making this method of treatment logical and without disadvantage.

5. Extracts to be used for skin testing (and the glycerolated extract cannot be used intradermally, as it is too irritating) can readily be made from concentrates.

6. Slowness of absorption—the 50 per cent glycerolated extracts take a longer time to be absorbed from the tissues than the aqueous extract, because constitutionals do not occur as generally or as rapidly as with the aqueous.

7. In comparing the results in a series of 51 patients, treated in 1932, with the results obtained in the same patients in 1931, we have found almost without exception that the results with glycerolated extracts were decidedly better (Table I). So much were we impressed with this feature that we are using glycerolated extracts, in all our hay fever cases: spring, summer, or fall types. We use the aqueous extracts for testing only.

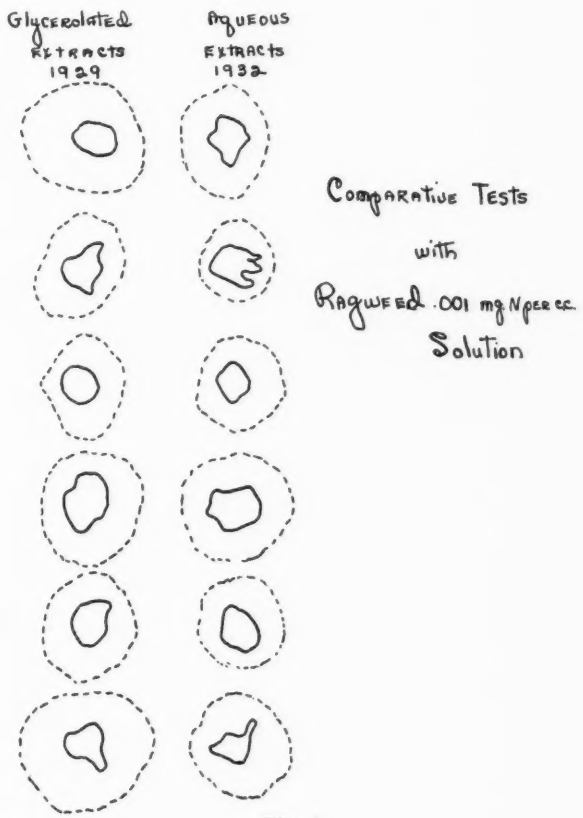

Fig. 1.

DISADVANTAGES

1. Viscosity: Fifty per cent glycerolated extracts are viscous, but we have experienced no difficulty in using this concentration of glycerin with the 26 gauge needle, which is generally used with aqueous extracts.

2. Pain of injections: Glycerin extracts are painful to some people, but the pain lasts usually only a few seconds and personally we have not had a single patient insist on its discontinuance because of this feature.

3. Marked local reactions do occur with glycerin, but this can be reduced considerably by decreasing the volume of extract to be in-

TABLE I

COMPARISON OF GLYCEROLATED WITH NONGLYCEROLATED EXTRACTS IN THE TREATMENT OF HAY FEVER

NUMBER	CASE NUMBER	AGE	SEX	DURATION YEARS	CLASS	MAXIMUM DOSE C.C.		NUMBER INJECTIONS		CONSTITUTIONAL REACTIONS		RESULTS % IMPROVED		REMARKS
						1932	1931	1932	1931	1932	1931	1932	1931	
1	112	32	M	14	C	0.1	0.065	20	23	None	None	85	85	
2	134	30	F	12	B	0.025	0.025	19	25	None	None	100	90	
3	521	19	M	15	BC	0.05	0.05	22	24	None	None	90	80	Marked local reactions at first
4	583	40	M	25	C	0.1	0.1	13	18	None	None	100	90	
5	584	15	M	5	B	0.015	0.005	18	20	None	None	90	90	
6	713	30	M	12	B	0.03	0.025	19	22	None	None	90	80	1932 best year
7	714	41	M	13	C	0.1	0.1	17	18	None	None	90	90	
8	831	36	M	9	C	0.1	0.1	18	18	None	None	90	80	
9	843	49	M	20	C	0.1	0.04	17	25	None	None	100	100	
10	877	45	F	11	C	0.1	0.1	12	10	None	None	100	90	1932 best year
11	893	44	M	14	C	0.1	0.08	24	24	None	None	90	75	
12	973	29	M	8	C	0.05	0.05	12	19	None	None	90	75	
13	1001	9	M	5	B	0.01	0.008	18	21	None	None	90	75	
14	1036	30	M	7	B	0.03	0.0175	17	20	6/30/32 to 0.025 9/ 3/32 to 0.035	4/14/31 to R. 0.02 5/ 5/31 to R. 0.02	90	80	Marked reaction to glycerolated extract
15	1052	41	F	25	C	0.1	0.05	11	14	None	None	95	90	
16	1077	32	F	14	C	0.09	0.045	19	22	None	None	90	75	Pregnant summer of 1931, so underdosed
17	1118	34	M	14	C	0.06	0.055	19	24	None	None	100	95	
18	1225	24	F	6	C	0.06	0.08	18	25	None	None	90	80	
19	1231	21	M	5	C	0.07	0.045	21	25	None	None	90	80	
20	1233	23	M	5	C	0.075	0.04	20	23	None	None	90	90	
21	1238	10	M	3	B	0.02	0.05	16	20	None	None	100	95	
22	1249	18	M	11	C	0.1	0.1	15	25	None	None	90	75	
23	1251	46	M	33	C	0.1	0.05	19	25	None	None	90	75	
24	1281	30	F	5	BC	0.06	0.035	22	24	None	None	90	70	
25	1292	27	M	18	C	0.1	0.1	12	16	None	None	80	80	
26	1308	36	F	20	C	0.1	0.1	21	25	None	None	100	100	
27	1310	26	F	5	C	0.1	0.1	15	21	None	None	90	80	
28	1330	32	M	16	C	0.1	0.1	10	14	None	None	100	90	

TABLE I—CONT'D

NUMBER	CASE NUMBER	AGE	SEX	DURATION YEARS	CLASS	MAXIMUM DOSE C.C.		NUMBER INJECTIONS		CONSTITUTIONAL REACTIONS		RESULTS % IMPROVED		REMARKS
						1932	1931	1932	1931	1932	1931	1932	1931	
29	1335	9	M	5	B	0.03	0.01	18	17	None	None	85	75	
30	1341	34	M	8	BC	0.06	0.1	16	16	None	4/24/31 to R. 0.01 mod.	90	80	
31	1397	43	F	12	C	0.1	0.1	16	21	None	None	95	50	Seasonal asthma mild in 1931 for 12 days. None in 1932
32	1414	9	M	4	B	0.03	0.01	18	16	None	None	100	90	
33	1415	36	M	8	C	0.1	0.1	21	19	None	None	95	95	
34	1421	32	F	5	C	0.06	0.02	21	25	None	None	75	75	
35	1425	38	M	30	C	0.1	0.1	25	25	None	None	100	85	
36	1426	14	M	8	C	0.1	0.1	14	25	None	None	90	80	
37	1431	51	M	10	C	0.1	0.085	20	23	None	None	100	90	
38	1447	40	M	14	C	0.1	0.075	17	24	None	None	85	70	
39	1457	33	F	17	C	0.075	0.08	15	23	12/2/32 to R. 0.075 8/2/32 to 0.075 9/2/32 to R. 0.075	4/10/31-0.085 7/ 2/31 } to 7/15/31 } R. 0.075 2/ 4/32 }	85	70	All constitutionals mild
40	1462	32	M	5	C	0.1	0.1	25	26	None	None	90	60	
41	1523	30	M	11	C	0.1	0.08	18	27	None	None	95	80	
42	1524	52	M	4	C	0.1	0.06	24	26	None	None	95	80	
43	1527	45	M	10	C	0.1	0.08	18	25	None	None	80	100	Best year 1931
44	1529	22	F	14	C	0.1	0.05	15	25	None	None	100	80	
45	1542	24	M	11	BC	0.075	0.05	17	25	None	4/28/31 to 0.09 mild	95	80	
46	1545	31	M	8	C	0.05	0.08	15	22	7/ 5/32 0.06 mild 7/29/32 0.075 mild	11/20/31 to R. 0.03 mild	75	50	
47	1547	75	F	27	C	0.1	0.08	16	22	None	None	80	80	
48	1565	32	F	4	B	0.025	0.02	16	21	None	None	85	50	
49	1567	9	M	5	B	0.03	0.01	24	20	None	None	80	60	
50	1581	16	M	9	C	0.04	0.01	17	18	None	None	90	75	
51	1584	24	F	4	AB	0.02	0.01	20	15	5/16/32 0.004 mild	None	95	50	
Total								888	1096	8	9			

jected. The maximum volume we use is 0.33 c.c., and using dilutions 0.0001, 0.0005, 0.001, 0.005, 0.01, 0.05, 0.1, and 0.3 mg N per c.c., we can limit the amount to small doses very readily. As a matter of fact, it is the local reactions that also help reduce the number and the severity of constitutional reactions.

CONCLUSIONS

1. Fifty per cent glycerolated ragweed extracts were used in a series of 51 late hay fever cases, and compared with results obtained in the same cases treated with aqueous extract in 1931.
2. Constitutional reactions were as frequent but much milder.
3. Results were much better.

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FURTHER OBSERVATIONS ON THE CHANGES IN SKIN TESTS FOLLOWING SPECIFIC POLLEN THERAPY*

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A YEAR ago before the Society for the Study of Asthma and Allied Conditions, one of us (Colmes)[1] presented evidence to show that the successful treatment of hay fever was often accompanied by a reduction in the degree of skin sensitiveness when tested by serial dilutions of pollen extract. In the discussion, however, the other of us maintained that in many patients the size of skin tests might remain the same at the end of treatment as it was in the beginning even though the hay fever was markedly relieved by the treatment. Since that time we have studied the problem in a larger number of cases, and we present our further observations as follows:

The patients fall into two equal groups (C and R) according to certain differences in the details and the policies of treatment. In the "C" series, the stock pollen extract was made by extracting 2 grams of ragweed pollen in 100 c.c. of a mixture of 54 per cent Coca's fluid and 46 per cent glycerin. From this stock, dilutions were made as needed. Skin tests were made by the scratch method using serial dilutions from 1:100 to 1:10,000. During the course of treatment, the size of the next dose and the length of the intervals between doses were determined in each case by the size of the local reaction from the last dose. The object of treatment was to bring about a reduction in the size of the skin tests, and with this idea the doses were continued until a repetition of the skin tests showed at least a smaller and better an absent reaction. In this series, 75 of the 121 patients were treated by the ordinary preseasonal method beginning in April, May or June, ten to fourteen weeks before the time of ragweed pollination, while 46 patients were treated by the perennial method. The "C" patients received an average of 23 doses.

In the "R" series, the stock material was a 1:100 extract of ragweed in Coca's fluid with no glycerin added. Skin tests with serial dilutions were made at the beginning of treatment, and the size of the initial doses was guided by them. Later doses were determined by the local reactions to the previous dose and in older patients by the experience in previous years, the old record becoming a very useful and very important guide in treatment. In this series, no definite at-

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tempt was made to reach the highest possible dose, and little attention was paid to the relative size of repeated skin tests, since the principle of optimal doses as described previously[2] was considered sound. All the patients in the "R" series were treated preseasonally and none of them perenially. They received an average of only 13 doses.

The two series of cases were of exactly the same size. The results of treatment are summarized in Tables I and II. Table I shows a

TABLE I

GROSS RESULTS IN TWO SERIES OF PATIENTS ALL WITH RAGWEED HAY FEVER

	TOTAL NO. CASES	NO. DOSES PER CASE	TOTAL GOOD RESULTS	SKIN TESTS SMALLER
			cases	cases
C Series	121	23	101 (84%)	106 (87%)
R Series	120	13	91 (76%)	69 (58%)
Total	241	18	192 (80%)	175 (72%)

TABLE II

END-RESULTS COMPARED WITH CHANGES IN SIZE OF SKIN TESTS

	GOOD RESULTS WITH		POOR RESULTS WITH	
	TESTS SMALLER	TESTS SAME	TESTS SMALLER	TESTS SAME
C Series	90 cases	11 cases	16 cases	4 cases
R Series	58	33	11	18
Total	148	44	27	22
	192 (80%)		49 (20%)	

number of points: Good results including "marked" as well as "complete" relief were obtained in a total of 101 cases, or 84 per cent, of the "C" series but in only 91, or 76 per cent, of the "R" series; in an average of 80 per cent for all. In comparison with this, the skin tests became smaller in 106 cases, or 87 per cent, of the "C" series and in 69 cases, or 58 per cent, of the "R" series. Table II shows the relation between the end-result and the changes in skin test. In the "C" series, out of the 101 cases with good results 90 cases (or 90 per cent) showed smaller tests, but at the same time, good results without change in the skin tests occurred in 11 cases (or 9 per cent). In the "R" series, however, only 58 cases (or 63 per cent) of the 91 good results showed a diminution of the tests while in 33 instances (or 36 per cent), the good results occurred without corresponding change, and in one or two of these the tests were even larger after the treatment than before it. Moreover, 8 of the 33 patients in this subgroup were completely relieved of their hay fever. The combined figures show that of the 192 good results, the skin tests became smaller in only 148 cases (or 77 per cent) whereas they remained of the same size or became larger in 44 cases (or 23 per cent). In the meantime,

poor results were obtained in a total in both series of 49 cases. Here the interesting point is not that the tests remained the same in 22 cases, but that in spite of the poor results, 27 of the 49 cases (or 55 per cent) showed a diminution in the size of skin tests after the treatment. With regard to all the cases together, this number constitutes only 11 per cent, but even so, the fact that there should be any cases at all in this group should not be overlooked.

TABLE III

C SERIES. GOOD RESULTS ONLY

SIZE OF SKIN TESTS BEFORE AND AFTER TREATMENT COMPARED

		SIZE OF TESTS BEFORE R/				
TESTS AFTER R/		XXXX	XXX	XX	X	TOTAL
	XXXX					0
	XXX	6	4	1		11
	XX	13	2	4		19
	X	10	11	7	2	30
	0	7	6	14	14	41
	Total	36	23	26	16	101

The figures in the lower line (of zero) in Table III and IV show the number of tests which have disappeared entirely. The figures underlined show the number of cases in which the tests remained the same. Other figures below these show the number of diminished tests and the degree of change. In one case the test was larger after treatment than before.

TABLE IV

R SERIES. GOOD RESULTS ONLY

SIZE OF SKIN TESTS BEFORE AND AFTER TREATMENT COMPARED

		SIZE OF TESTS BEFORE R/				
TESTS AFTER R/		XXXX	XXX	XX	X	TOTAL
	XXXX	7	–	–	–	7
	XXX	10	15	–	1	26
	XX	3	10	8	–	21
	X	4	11	15	3	33
	0	0	1	0	3	4
	Total	24	37	23	7	91

How great is the reduction in skin tests? Tables III and IV attempt to show this in a graphic manner* The skin tests disappeared completely in 40 per cent of the "C" series but in only 4 per cent of the "R" series, and correspondingly, reductions of two places are more numerous in the "C" than in the "R" series.

In this study, all tests have been made by the scratch method. When some of the patients were retested by the intracutaneous

*For each patient the clinical records showing the graphic drawings of the reactions resulting from scratches through serial dilutions were appraised in a uniform manner and such arbitrary values as "xxxx" and "x" were given to each set of tests The symbols are arranged in the tables so that the sizes of tests before treatment are plotted against the sizes of other tests made after treatment.

method, it was found that many of the tests were still positive when the customary dilutions were used. Later, however, it was found that if the dilutions could be carried far enough, that is, to dilutions of 1:100,000 or even 1:1,000,000, then definite reductions in the degree of sensitiveness could be demonstrated even by the intradermal method.

Several questions are suggested by the observations described. The first is whether or not the skin test has proved its value as a guide in hay fever therapy. The data show that a diminution of skin test occurs in a large majority of those hay fever patients whose treatment with pollen extract is successful. However, exceptions to this finding occur in two directions. First, good results may occur without change in the tests (18 per cent of the cases), and second, poor results are sometimes observed even though the skin tests are diminished (11 per cent of the cases). The frequency of these exceptions is not great, but it is enough to make it doubtful whether relief from hay fever and reduction of skin tests can depend upon a common basis.

As a matter of fact, all our clinical experience is against the direct correspondence of skin test size and severity of symptoms. In certain extreme cases, we find large skin tests to pollens in patients who have no clinical hay fever at the time of pollination. For example, there are many patients with New England hay fever who have positive tests to grasses but no symptoms in June, and we also find patients with severe hay fever but with no positive skin tests at all. If the relation between tests and symptoms was direct in each case, how simple the problem would be!

The second question is whether the reduction of the skin test depends upon the total amount of treatment or upon the size of the final doses reached in the course of treatment; whether the increasing tolerance of the subcutaneous tissue, as shown by smaller local reactions to larger doses, is accompanied by an increasing tolerance of the skin. The answer is "yes" in the majority of cases but not in all. A study of the "R" series shows that in the 58 cases with good results and smaller tests, the final dose was of the 1:100 dilution in 24 cases. It was of the 1:500 dilution in 21 cases; of the 1:1000 dilution in 12 cases; and only of the 1:5000 dilution in one case. This latter patient illustrates several interesting features, particularly the discrepancy between symptoms, tests and response to treatment.

CASE REPORT

Miss H. K. T., aged forty-eight years, weighed 180 pounds. She had had hay fever all her life, at first more in June and July, now limited essentially to August and September. In 1917, treatment with grass pollens and with ragweed extract had relieved her completely, and after that she had no great trouble and no further treatment for

seven years. In 1924, severe hay fever began on July 3 and lasted until July 25, disappearing when skin tests were made on that day. She had no other treatment in 1924. During the next years, she had some trouble in August and September but did not come for further treatment. In 1930, she was in San Francisco and well. In 1931, severe hay fever began on August 22 and she applied for treatment on September 1. Skin tests showed enormous reactions to both grasses and ragweed. Three small doses of ragweed did not help very much. In 1932, she was tested on June 24, and between then and

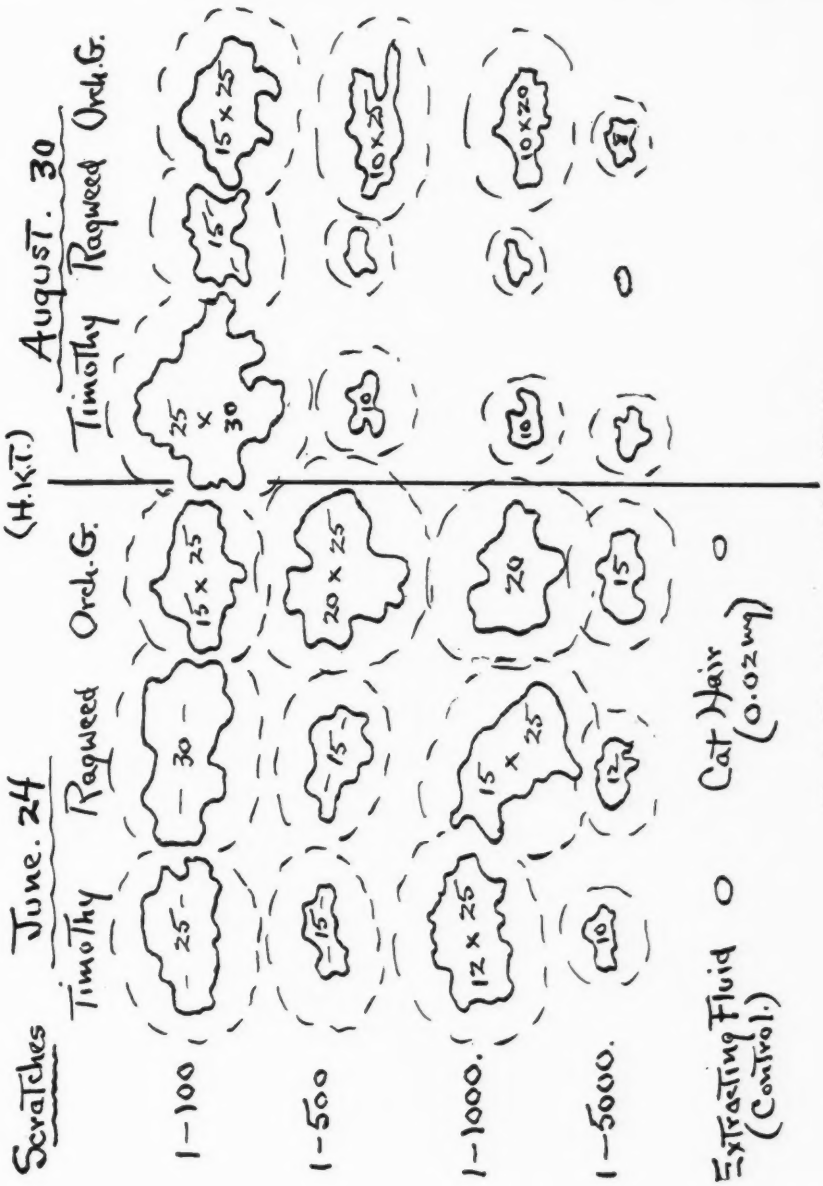

Fig. 1.—Diameters measured in millimeters.

August 30, she received 9 double doses of ragweed, the largest of which consisted only of 0.25 c.c. of the 1:5000 dilution. She had no hay fever at all in 1932.

The reproduction of the skin tests before and after this 1932 treatment is presented in Fig. 1. This shows first that symptoms may be slight although skin tests are large. This woman had no treatment and no symptoms in June or July and yet she had reactions to the grass pollens which were enormous. Possibly she might have done well without treatment with ragweed, but she had had symptoms from ragweed the year before, and it is fair to say that the treatment did help her. The reduction in the size of her tests is very small, but it is definite and is likewise attributable to the treatment because in the previous year at her first visit in September, 1931, the size of the tests then was quite the same as the size of the tests in June, 1932. This reduction occurs not only in the ragweed test but in the grass tests as well, and this leads to a third question: Is the reduction of skin tests a specific phenomenon?

In 1928 Lamson, Piness, and Miller[3] retested 106 patients at the end of treatment and found that while there was a diminution in the size of the skin test in 63 per cent, there was no change in 37 per cent. When pollens of a genus not used in treatment were used for retest, the tests to these other pollens were likewise reduced in 15 out of 20 observations.

In 1930 W. Storm Van Leeuwen found that treatment with one allergen does reduce the amount of reaction to other substances, provided only that the treatment produces local reactions. He postulated a "Zwischensubstanz" as a necessary feature of all reactions and as being uniform and common to them all. In describing it, he referred to Sir Thomas Lewis' H-substance and also to complement. He regarded it as a nonspecific factor common to all reactions noting first that complete desensitization to one substance will bring about diminished reactions to other substances, but second, that this other diminution will occur only in case the treatment has caused local reactions of definite extent.

Finally, the Report of the British Asthma Research Council for 1932 includes a statement by Gough of St. Mary's Hospital that "Whenever adequate dosage has been given, complete loss of the skin reactions to all the test grasses has resulted, no matter from which grass or grasses the vaccine has been constructed."

In our own work, we have frequently observed that treatment of patients with early hay fever with one or two grasses such as orchard grass and red top brought about a reduction in skin tests not only to the same grasses but also to other grasses, like timothy, at the same time. More striking, however, are other observations that in patients with double hay fever, sensitive to both grasses and ragweed,

the early treatment with the grasses alone, often brought a reduction in the skin tests to grasses, and whenever this occurred, the reaction to ragweed was reduced at the same time. Evidently then, the reduction of skin tests in hay fever is not necessarily a specific effect. It can be brought about in a nonspecific manner.

The relation between the reduction in skin tests and the improvement in symptoms requires further comment. Assuming that treatment of a patient with double hay fever with grasses may bring about a reduction in the skin test to ragweed, it is by no means certain that the patient would be relieved of his ragweed hay fever. The temptation to treat the "double" cases with ragweed is so strong that the question has not been answered by direct experiment. So far, all authors agree that the treatment of hay fever is a highly specific procedure and that the selection of the particular pollen, or at least the genus of the pollen, is an essential part of the technic. Perhaps, however, in the near future some one will treat a group of patients with those pollens which give positive skin reactions, but whose dates of appearance in the air do not correspond with the dates of symptoms. The results will be interesting.

As for the relation between skin tests and symptoms, it is evident that they go together with considerable correspondence in most of the cases. Discrepancies, however, are all too common. Patients may have large tests with no symptoms at all, or they may fail to show a skin test and yet have all the symptoms of a typical hay fever. Both these irregularities are important and interesting. They indicate that the relationship is only general at best.

While the skin test as now performed may be a useful guide in treatment, it is even at its best only a crude index of the degree of clinical sensitiveness. Improvements in present methods may be expected in the future. Further study of the pollen antigen may result in the development of test materials which will represent the active constituent of the pollen grain unmixed with all the other parts. Further study of the patient may demonstrate what we suspect already; that the degree of sensitiveness of the nasal mucosa is quite different from the degree of sensitiveness of the skin, just as the skin is different from the subcutaneous tissues.

In the meantime, our present data lead us to suggest that in allergic individuals there are two different levels of desensitization (of the whole body), one relatively low at which the nasal symptoms disappear, the other much higher which must be reached before the skin tests will change.

SUMMARY

1. Two groups of patients with ragweed hay fever were treated: one with an average of 23 doses per patient, the other with 13 doses.

2. In both groups good results in treatment were accompanied by a diminution of skin tests in a majority of the patients.

3. Good results without change in the skin tests occurred in 18 per cent of all the cases.

4. Poor results even though the skin tests were diminished occurred in 11 per cent of all the cases.

5. It is doubtful whether relief of symptoms and reduction of skin tests can depend upon a common basis.

6. The reduction of the skin test does not depend upon the size of the final dose.

7. The reduction of skin tests is not necessarily a specific effect.

8. The skin test as now performed is only a crude index of the degree of clinical sensitiveness.

9. It is, however, a useful guide in the treatment of hay fever.

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STATUS ASTHMATICUS OR SEVERE SUBACUTE ASTHMA*†

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THE acute and chronic forms of bronchial asthma are pretty generally recognized and understood. In the acute form the sufferer is perfectly normal during the intervals between paroxysms. In the chronic type there is never complete freedom, the lung capacity is more or less reduced at all times and is aggravated by reclining or exercise. Both these forms are compatible with the ordinary activities of life, the severer paroxysms being controlled by adrenalin, ephedrine, coal tar products, sprays, etc.

The purpose of this discussion is to call attention to a third form of great gravity which we believe has sufficient clinical characteristics to justify more intensive study under the term "status asthmaticus." Briefly, it is a period of very intense dyspnea lasting a few days to a week (occasionally longer) caused by an outpouring of very viscid mucus into the finer bronchioles, resulting in a very serious loss of lung capacity and a corresponding failure to respond to ordinary doses of adrenalin. Death is more common in this than in either of the other commoner types.

It is usually seen in those already suffering from continuous asthma, but it may follow a series of acute attacks and has been observed in pollen sensitive persons whose symptoms are limited to a definite season. The onset is gradual over a period of twenty-four to forty-eight hours. Larger doses and more frequent administration of adrenalin are required until finally the relief from this drug is slow and inadequate. There is a drawn, anxious expression to the face. Slight cyanosis appears. The pulse is fast and there are often extrasystoles. The blood pressure is usually moderately elevated, 150 mm. to 170 mm. systolic. Albumin appears in the urine and occasionally acetone and casts. There is a mild leucocytosis with polynuclears 70 per cent to 85 per cent and no eosinophiles.

The duration seems to be limited distinctly to three to four days, during which time the person is very weak. Exercise, even walking, is out of the question, and existence is simply one hypodermic after another. In the early stages there is little cough and almost no expectoration. What little is produced is gelatinous, will not pour or run and is usually loaded with eosinophiles.

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Status asthmaticus may terminate in one of four ways. First, it may terminate in death, usually from exhaustion rather than asphyxiation. Second, it may terminate rather rapidly in the course of twenty-four hours with abundant expectoration. Third, fever without localizing pulmonary signs may develop about the third day and last three to four days. The dyspnea, often extremely severe at the onset of the fever, disappears before the temperature returns to normal. Fourth, pulmonary consolidation with fever and leucocytosis may come on about the third or fourth day and run a course similar to pneumonia, but without the toxemia and cyanosis usually seen in this disease, a condition we speak of as asthmatic pneumonia. In our experience all patients with such pneumonias have recovered and this disease is usually followed by a period of freedom from asthma.

We believe the condition is due largely to the mechanical effect of the sudden outpouring of large quantities of this peculiar sputum. This is very viscid and sticky, rather than slimy, and is similar to that seen in postoperative or posttraumatic atelectasis. When there is an opportunity to examine this sputum at postmortem, it is seen to be even more viscid and can be forced out of the two to three millimeter bronchioles like a gelatinous earthworm. We believe the reason atelectasis does not develop more frequently in asthma is because of the greater activity of the lungs. Local obstructive emphysema is more common and almost always precedes pneumonia when this develops.

This obstruction of the bronchi must result in absorption of dammed up, partically decomposed sputum. Depending on the individual, this reabsorption is probably the cause of much of the distress of the patient, as it is in the postoperative atelectasis cases. The mechanical blocking of the air passages is not enough to explain the dyspnea, because cyanosis, while common, is rarely marked. Furthermore, the patient can usually hold his breath during examination of the heart.

The physical signs give a very good guide to the progress of the disease. Early in the course, in addition to the dry, musical râles of asthma, moist râles of varying degrees appear in scattered areas, the location changing from time to time. They are often heard only during the relief period after adrenalin. One of the favorite spots is the anterior tip of each lower lobe, but more particularly of the left.

At this time the intensity of the breath sounds varies from lobule to lobule, being loud and clear at one spot and distant and musical one inch away. As the condition progresses, larger areas, often a whole lobe, become involved, and the breath sounds are either absent or very much diminished. Now for the first time we get signs other than by auscultation. Inspection will often reveal an increase in size with diminished expansion, and the percussion note is almost tympanic—a true obstructive emphysema. After adrenalin the breath sounds

often come through in varying intensity with both moist and musical râles. When adrenalin fails to clear the lung, dullness and bronchial breathing may follow with the development of pneumonia. As the condition clears up by liquefaction of the sputum, moist râles of varying degrees appear over the areas where the breath sounds were diminished. This phase is of short duration, usually not over two days.

Therapy should be directed first toward keeping the air passages open temporarily and second to liquefying the sputum. No single drug is efficacious in this asthmatic emergency. The condition must run its course, and our duty is to use drugs judiciously and courageously to aid the patient's natural fighting processes.

Adrenalin is the best single remedy which we have at our disposal for increasing the lumen of the bronchi. In status asthmaticus we are often told by the patient that adrenalin has lost its effect, and this is too often apparently true. We have given four one c.c. doses of adrenalin to a fourteen-year-old girl of frail physique without producing the usual trembling and headache from overdosage with adrenalin. To an elderly man we have given 1.7 c.c. every two or three hours without any trembling and ten days later, after the status asthmaticus had passed, the man has complained about the unpleasant effects of 0.6 c.c. twice a day. This same man is today getting complete relief with 0.2 c.c. Fixation or neutralization of adrenalin must take place during the height of the attack.

In addition to the usual "p. r. n." order for adrenalin we have found small doses, 0.3 c.c. to 0.6 c.c., administered every hour to be very efficacious and often eliminate entirely the dyspneic crises which come on four or five times in twenty-four hours. These small hourly doses are given even if the dyspnea is very slight.

Morphine should be used sparingly, but is invaluable at times. It should never be used in doses which cause vomiting, slowness of the respiratory rate or elimination of the cough reflex. These unfortunate individuals must breathe hard and cough if they are to keep their bronchi open. Morphine should be used only to give the patient mental rest and physical relief from excessive and exhausting cough. We do not believe it has any effect whatever on the asthma as measured by the lumen of the bronchi. Certainly the auscultatory signs are not changed by morphine. We are accustomed, in those who are receiving hourly doses of adrenalin to give a small dose of morphine in the late evening to give them relief at night. During dyspneic crises morphine in small doses may be added to the adrenalin.

Atropine should never be used. If it does anything, it dries up the membranes and makes the viscid sputum thicker. Ammonium chloride has been disappointing. Ephedrine and stramonium are too slow and weak.

We find that the best drug for liquefying sputum is potassium iodide used in 20 or 30 grains as an initial dose, followed by 10 grains three times a day. The coal tar products are often of value, but care must be used to be sure the patient is not sensitive to these drugs. This can best be obtained from the history, as there are few persons who have never taken aspirin. Barbiturates, we believe, often aggravate the condition without bringing on a sudden increase in symptoms. The bromides in large doses seem to work as well.

Hypodermic injection of solutions of a specific substance to which the person is sensitive (such as ragweed) should be used with great caution. They are probably of some value, but once the status asthmaticus has been well established, it must run its course. Elimination of the offending substance is of course urgently indicated. The patient should be kept as free from all dusts as possible, but the usual rapid phylactic or coseasonal treatment should not be attempted.

If pus be present in an antrum, this should be evacuated, but extensive operative work is out of the question. Vaccine likewise should be administered with great care and in small doses. We believe it can grievously aggravate the symptoms.

The pulse is practically always fast, usually well over one hundred, occasionally up to 160. We usually do not use digitalis until extrasystoles appear, at which time it is given in large doses.

The patient should be given absolute mental and physical rest, preferably in the hospital. The diet should be soft and easily digested. It should be given in small quantities. The bowels should be kept open, and this can best be done with small enemas rather than with drugs. The kidneys seem to need little attention in spite of an almost constant albuminuria.

Many of these persons have hypertension. The asthma aggravates the hypertension, so that adrenalin, in relieving the asthma, lowers the blood pressure. Certainly hypertension is no contraindication to the use of adrenalin.

In conclusion, we believe that the subacute form of asthma has sufficient distinguishing characteristics in its symptoms and course to justify special study and consideration under the term "status asthmaticus."

ALLERGY A CONSTANT FACTOR IN THE ETIOLOGY OF SO-CALLED MUCOUS NASAL POLYPS*†

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ALTHOUGH infection has been the generally accepted primary etiologic factor of so-called mucous nasal polyps, dissatisfaction with this viewpoint has been expressed in the last thirty-four years by a number of observers. Of these, several have suggested the existence of a common underlying constitutional factor, as yet unknown in character. We wish to present clinical data which we feel warrant the conclusion that this underlying constitutional factor in the causation of polyps is allergy.

HISTORICAL

The evolution of thought concerning nasal polyps has been admirably traced by Hirsch,[1] to whose contribution we are greatly indebted. In ancient writings, the term polyp was applied generally to all nasal tumors, but during the middle ages was restricted to soft tumors alone. Billroth[2] in 1855, with the added authority of microscopic studies, was able to differentiate between soft polyps (mucous polyps), cystic polyps, fibrous or sarcomatous polyps and carcinomatous polyps, recognizing their common origin from the mucous membrane and their common possession of the component structures of normal mucosa. He furthermore associated a definite anatomical structure with the term "mucous polyp" and from histologic studies recognized that such polyps represent a true hypertrophy of the mucous membrane in all its parts.

Zuckerkandl[3] in 1882, on the basis of macroscopic differences, suggested a classification including genuine nasal polyps, hypertrophies of the nasal mucous membrane resulting in papillomatous or larger edematous swellings on the lateral nasal wall, polypoid hypertrophies on the posterior ends of turbinates, and papillomas. He emphasized the separation of true nasal polyps from the other soft swellings of the nose. He suggested that they were the result of inflammation of the mucosa and gave the first accurate description of their sites of origin. He stated that polyps develop principally in the respiratory zone of the nasal cavity: (1) on the edge of the hiatus semilunaris, (2) in the infundibulum, (3) at the ethmoidal ostia, (4) at the ostium frontale, (5) at the ostium maxillare, (6) on the edge of the middle

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turbinate, (7) on the edges of accessory furrows on the medial side of the middle turbinate, (8) on the ethmoidal bulla, and (9) in the ethmoidal cells.

Hopmann[4] in 1885 classified soft growths occurring on the turbinates and the lateral wall as follows: (1) edematous fibroma or mucous polyp, (2) polypoid hyperplasia or glandular polyp, (3) papilloma or mulberry polyp, and gave accurate gross and microscopic descriptions of each type. His classification with minor changes is the one accepted today. He further pointed out the fallacy of the terms "myxomatous" and "mucous" as applied to the first mentioned group, when he showed chemically that so-called mucous polyps do not contain mucus but on the contrary chiefly albumin. He therefore preferred to use the term "edematous fibroma."

Hirsch[1] in 1927 advanced the view that mucous polyps practically always originate in the sinuses, most frequently in the antrum, and next in frequency in the sphenoidal, ethmoidal and frontal sinus in the order named. He believes that the prolapse of the catarrhal mucous membrane of the sinus through the ostium is followed by incarceration of peaks of mucous membrane. However, he believes that at times a sagging of the nasal mucous membrane itself may result from an extension of the sinus inflammation to the nose. He states that all recurring polyps must lie in the vicinity of the accessory sinus openings, but that while this location holds for the great majority of polyps, it does not hold for all.

CLASSIFICATION OF POLYPS

Nasal polyps, other than malignant forms, may be classified as follows:

1. *Mucous polyp or edematous fibroma* (a better term we feel is *myxoid fibroma*).
2. *Mixed polypoid hyperplasia.*
3. *Papillary hypertrophy or mulberry polyp.*

1. *Mucous polyps or edematous fibromas (myxoid fibromas)* may be single or multiple. They are usually but not exclusively pedunculated. Their base is in close relation to the ostia of the sinuses from which, as Hirsch pointed out, they usually spring. They are smooth, pale, translucent, often glassy in appearance. Their color varies from a translucent white or gray to bright yellow, tinged with red. In older polyps, however, subjected for long periods of time to dust or irritants, there may be marked discoloration. They possess a characteristic jellylike softness, and their consistency at times is such that unless palpated by a probe they may be mistaken for mucus. Their serum content is readily expressed, leaving an insignificant tag.

Microscopically, there are hypertrophy and edema of the tissue from which the polyp has arisen, but as pointed out by Hopmann, the mu-

cous polyp, although arising from mucous membrane, lacks entirely, or presents only in scanty remains, that most striking histologic structure of mucous membrane, the mucous gland. The epithelium varies from a thin layer of columnar cells to a thick, many-celled layer of stratified columnar epithelium. The conversion of elements into mucus-containing goblet cells is much less frequent than in normal membranes, and degeneration of goblet cells is wide spread. Ciliated cells become increasingly rare in the older polyps. The bulk of the polyp consists of an edematous tunica propria, with large areolar tissue spaces containing a considerable quantity of albuminous fluid and showing a tendency to cyst formation. The areolar fibers are loosely disposed, crossing in all directions and enclosing correspondingly indefinite lymphatic clefts. The cellular constituents are relatively inconspicuous and are bathed by the fluid which wells through the interfascicular spaces. Within these clefts are also lodged the migratory lymphocytes, round cells, plasma cells, mononuclear cells and eosinophiles. Glands are usually sparse, due to pressure atrophy. The vessels are thin walled and composed of smaller channels of the superficial reticular zone rather than deeper ones of larger lacunae. Nerve filaments are rare. When the process has extended deeply, an exostosis of the bone may be present at the site of the polyp.

It is the mucous polyp which is the subject of our discussion.

2. *Mixed polypoid hyperplasia*, as Kaufmann[3] points out, is essentially similar in structure to the mucosa but is more markedly cellular. Its color is red or grayish red. Alagna (cited by Kaufmann) calls this type, granulomatous polyp. This group may be subdivided into (a) *glandular hyperplasia or glandular polyp*, and (b) *angiomatous hyperplasia or angiomatous polyp*.

Glandular hyperplasia or glandular polyps, as described by Hopmann,[4] are a dense, vascular formation. They are usually red in color and retain their form upon pressure. Histologically, they differ from mucous polyps by being rich in glands and infiltrated with cells, and by having as exclusive origin from the turbinates themselves, especially the middle and to a lesser extent the inferior. By presenting a body separable from the mucous membrane and by being movable with a probe, they may be distinguished from hyperplasia following hypertrophic rhinitis.

Angiomatous polyps comprise a small group of highly vascular lesions of obvious characteristics.

3. *Papillary hypertrophy or mulberry polyp* is differentiated by Hopmann primarily by its papillary form. It appears principally on the posterior end of the inferior turbinate, and the mass consists of hyperplasia of the turbinal mucous membrane in which cystic degeneration of the glands and dilatation of the vessels have occurred. This type

has by some been considered as a mixed or combination form of glandular and angiomatous polyp mentioned in the preceding section. Its papillary structure, its usually red color and its comparatively firm structure readily differentiate the mulberry or raspberry from the mucous polyp.

THEORIES ON THE ETIOLOGY OF SO-CALLED MUCOUS POLYPS

Various causes of mucous nasal polyps have been proposed and defended from time to time. That none has received complete acceptance is shown by the fact that in the recently published *Standard Classified Nomenclature of Disease*,[6] mucous polyps are classified under conditions of obscure etiology. Those theories which have received the greatest consideration and the widest acceptance will be referred to in some detail. One fact is generally accepted: mucous polyps do not occur congenitally. Zuckerkandl[3] in many hundreds of dissections of the newborn failed to find either hypertrophy or the beginnings of polyps.

Inflammation Theory.—The inflammatory origin is perhaps the most widely accepted as well as one of the earliest theories advanced. Friedrich[7] in 1858 attributed the origin of mucous polyps to long-standing coryza. Störk[8] in 1880 also suggested prolonged nasal catarrh as a cause. A similar view was expressed by Chiari[9] and by Scheff[10] in 1886, both of whom, however, suggest a certain predisposition as a necessary factor. Wright[11] in 1897 also stressed the inflammation theory. Zuckerkandl in support of the theory of the inflammatory character of mucous polyps pointed out that the relation of the stroma and the exudate in nasal polyps was the same as in catarrhal disease of the antral mucous membrane. Polyps and catarrhal inflammations of the antrum were conceived as identical processes. He believed that polyps could develop because of chronic irritation and offered as proof of this statement the fact that polyps develop about rhinoliths and that the nasal mucous membrane in contact with a rhinolith presents an undoubted localized rhinitis. Another point advanced by Zuckerkandl in favor of the inflammatory origin of polyps was the lack of sharp demarcation at the base of polyps and the gradual merging into physiologic tissue.

The nasal inflammation has usually been attributed to infection, so that more recent writers speak of the infectious origin of mucous polyps. Thomson[12] in 1926 expressed the view that suppurations of all kinds in the nose are the chief immediate cause of polyps. Barnhill[13] in 1928 stated that polyps are probably always the result of infection. In the same year, Ewing[14] states that while a special predisposition may exist in the etiology of polyps, the growths are adequately explained as the result of chronic inflammation and the irritation of retained secretion.

A new turn was given to the inflammation theory by Woakes[15] in 1885 when he described a disease of the ethmoid bone leading to the necrosis of bony flakes *(necrotizing ethmoiditis)* which in turn gives rise to polyp formation. Cholewa[16] in 1900 and Kassel[17] expressed themselves in agreement with Woakes. These views were supported in part and elaborated by Hajek[18] who subdivided the inflammations of the mucosa covering the ethmoid into three groups: (1) a superficial inflammation confined to the surface layers of the mucosa and associated principally with simple hypertrophy as seen in nasal catarrh; (2) a deep inflammation, extending down to the periosteum and into the open medullary spaces of the bone, associated with changes ranging from mild hypertrophy to high grade polypoid degeneration; (3) actual involvement of bone, clinically showing the most marked changes in the middle turbinates and at the points of insertion of the polyps. In all cases Hajek believed that the inflammation began on the surface and extended downward, eventually to involve the bone, rather than beginning as a primary osteitis as proposed by Woakes. According to Hajek, polyps begin as edematous hypertrophies of the mucosa, inflammatory in origin: the process may remain limited to the surface or may penetrate to the deeper layers. He pointed out that the inflammatory changes were most marked in the superficial layers and that the growth of the polyps stops with the cessation of the primary irritative factor, such as empyema or foreign body.

Cordes[19] in 1901 on the basis of extensive pathologic studies expressed agreement with Hajek's classification, but was inclined to support the view of Woakes that recurring polyps are invariably on the basis of bone necrosis. Uffenorde,[20] on the other hand, in 1907 reported microscopic studies in 80 cases of ethmoid disease which confirmed the findings of Hajek in all essentials.

Sinus suppuration as the starting point of mucous polyps was first proposed by Kaufmann[21] in 1890, who believed that in many cases empyema of the antrum was the sole cause of the development of the polyps within the nose. Grünwald[22] in 1893 was emphatically in favor of an etiologic relationship between suppurative sinusitis and polyp formation and concluded that nasal polyps are practically pathognomonic of sinus empyema. In 82 cases of polyp formation he found sinus suppuration in 71. Polyps did not reappear after the empyema was cured. He felt that caries of the bone and polyp formation were both effects of the sinus suppuration. Similar views have been expressed, among others, by Shurly[23] in 1900, Turner[24] in 1924, and by McCaskey[25] in 1931. Hirsch[1] who, as previously stated, propounded the view that the original source of polyps is practically always in the sinuses, at first also subscribed to an inflammatory etiology.

Opposition to the view that sinus suppuration causes polyps was expressed by Fränkel[26] in 1896. Among many autopsies on subjects with

sinus suppuration, he found no nasal polyps in spite of the fact that in many instances the infection had been present for a long time. He stated flatly that the finding of polyps by no means justified the assumption of preexisting sinus disease. Alexander[27] in 1896, expressed a similar view because in 104 cases of polyps he found only 35 with empyema, whereas in 170 cases of empyema polyps were present in only 44. Wertheim[28] in 1905 reported the finding of nasal polyps at autopsy in only 7 per cent of 165 cases of sinus disease, whereas polyps were found eight times in the absence of sinus suppuration. Skillern[29] in 1910 pointed out that polyp formation may occur without suppuration. Hajek[30] in 1915 reiterated his view that polyps are not pathognomonic of sinus infection, pointing out that in certain of his cases suppuration of the sinuses secondarily complicated a polyposis that had been present for years. As recently as 1926[31] he stated that nasal polyps are the typical products of chronic inflammation of the covering of the ethmoid bone. Pierce-Brown[32] in 1900 stated his conviction that the etiology of polyps cannot be confined to any one cause: "In the large majority of cases where polypi were large and numerous, there was no sinus disease. On the other hand, cases of antral disease that I have attended were usually affected also with polypi of the adjoining middle turbinate but these polypi were usually small. After healing of the sinus, the polypi failed to return."

A vascular origin for mucous polyps was suggested by Coakley[33] as early as 1899, when he stated that polyps may occur independently of suppuration, and expressed the view that vasomotor disturbances may account for some of the cases. Yonge[34] in 1907 expressed the belief that cystic dilatation of glandular ducts produces obstruction of circulation in veins and capillaries and this in turn leads to serous infiltration of the tissues. Williamson[35] suggests that polyp formation is due in part, at least, to the peculiar anatomic arrangement of the blood vessels found in the nose: vascular channels run a long course beneath a highly active secreting membrane which is closely applied, without intervening tissue, to a hard bony, cartilaginous or fibrous base: conditions under which inflammation leads readily to stasis, engorgement and tissue hypertrophy.

Lymph-vascular disease has been invoked as a cause by Williams[36] who suggests that there is an infectious lymphangitis with tissue changes analogous to elephantiasis. The lack of cellularity of polyps is an obvious objection to this view.

The constitutional or hereditary factor has been suggested from time to time since the earliest writings on the subject, largely, it would appear, in an attempt to explain the discrepancies between clinical observation and other theories of origin. Heymann,[37] Moure[38] and Uffenorde[39] have expressed this view. More recently Runge[40] has said:

"To interpret all of these pathological findings as the result of a productive inflammation arising in a fundamentally normal mucosa, seems to me to be untenable. The development of polyposis demands in my opinion the preexistence of a general pathologic alteration of the mucosa, the 'hyperplastic mucosal constitution.'"

ALLERGY IN THE ETIOLOGY OF MUCOUS POLYPS

In his admirable clinical and histopathologic studies of the nose in allergy, Hansel[41] pointed out that the changes in the nose and sinuses in allergy are similar in every respect to those which occur in the bronchial structures in bronchial asthma. His opinion seems to be that the changes in the mucosa including the polyps, as found in allergic disease, have primarily an allergic etiology. He is, however, unwilling to accept the idea that the rôle of infective bacteria in helping to produce these changes is of the nature of true bacterial allergy, but that these organisms must be considered purely as secondary invaders. He therefore does not extend the presence of an allergic factor into the etiology of all mucous polyps and points out that allergic sinus disease with secondary infection should be differentiated from primary sinus infection with polyps.

Hirsch[42] more recently has gone farther, stating that it is his clinical impression that all mucous polyps may be based on allergy. However, he has not adduced any clinical or other proof for his opinion.

We wish to present clinical data which would seem to show that allergy is invariably present as a factor in the causation of mucous polyps.

TABLE I

CLINICAL INCIDENCE OF MUCOUS POLYPS IN ALLERGIC STATES

	TOTAL CASES	NUMBER WITH POLYPS	PERCENTAGE
Bronchial asthma	500	148	29.6
Vasomotor rhinitis	73	10	13.7
Hay fever (seasonal)	98	13	13.2
Hay fever + perennial asthma	31	9	29.0

The incidence of nasal mucous polyps is strikingly high in allergic diseases of the respiratory tract. The incidence is highest in those cases in which the allergic state continues throughout the year. While 30 per cent of asthmatics are found to have polyps on intranasal inspection, it is probably true that an even higher percentage would be found to have polyps if the interior of the sinuses could be inspected. Thus of 50 asthmatic patients who were subjected to the Caldwell-Luc operation, 34 showed polyps on intranasal inspection; all 34 were found to have antral polyps as well, and an additional 10 had antral polyps in the absence of nasal polyps. Conversely, the incidence of

polyps is lowest in that allergic condition in which the sensitizing substance acts upon the nasal mucosa for only a short time each year: seasonal hay fever. Furthermore, the seemingly equal incidence of polyps in seasonal hay fever and vasomotor rhinitis as set down in Table I is more apparent than real. Roentgenologic examination in 50 seasonal hay fever patients showed sinus abnormality 74 per cent[43] —an incidence no greater than in our series of 50 controls[44]—whereas 90 per cent of 40 vasomotor rhinitis cases showed roentgenologic abnormalities and with a larger number of sinuses involved per patient.

TABLE II

CLINICAL INCIDENCE OF MUCOUS POLYPS IN ROUTINE EXAMINATIONS OF PATIENTS WITH NONALLERGIC DISEASE AS MAJOR COMPLAINT

PRESENTING DISEASE	TOTAL CASES	NUMBER WITH POLYPS	POLYPOID DEGENERATION OF THE MUCOSA
Bronchiectasis	64	1	3
Lung abscess	15	0	0
Pulmonary tuberculosis	82	6	1
Arthritis	200	7	1

The incidence of nasal polyps is extremely small in patients whose presenting symptoms are those of nonallergic diseases. We have been interested for some time in the relation of paranasal sinus disease to diseases of the lower respiratory tract as well as diseases elsewhere in the body. We were soon struck with the relative paucity of nasal polyps in connection with other respiratory conditions, in spite of the overwhelming presence of sinus infection in some of these states. Thus in 64 cases of bronchiectasis, a condition in which 100 per cent of our cases showed roentgenologic evidence of sinus disease, usually a pansinusitis with dense clouding of the sinuses involved, we found only a single patient with definite mucous polyps. It therefore seemed highly questionable to us that infection was the sole etiologic factor in the production of polyps. So we determined to search out the incidence of mucous polyps in a considerable series of patients suffering primarily with nonallergic diseases and then to investigate further from the standpoint of a possible unsuspected allergy those individuals found to have polyps. Of 372 patients with pulmonary tuberculosis as diagnosed in the Medical Division of the Hospital of the University of Pennsylvania, 82 gave sufficient evidence of nasal abnormality to lead to a clinical examination of the nose by a rhinologist. Mucous polyps were found in 6. Yet 45 of these patients, especially those with cavitation, mixed infection and profuse sputum, had evidence of sinus disease which in many instances was most extensive. Of 200 patients with chronic arthritis in whom an intranasal examination was made in a search for focal infection, 7 were found to have mucous polyps. Yet 80 patients were found to have sinus abnormality clinically or roent-

genologically. Of 15 cases of lung abscess, all with extensive sinus disease, none had polyps.

In our table we have also listed those cases in which the examiner said that he found "polypoid degeneration of the mucosa." Unfortunately he did not always state whether he was dealing with a pale, edematous lesion allied to or possibly the forerunner of true mucous polyp formation, or with the red, thickened, firm mucosa of an inflammatory process.

TABLE III

ANALYSIS OF POLYP AND POLYPOID DEGENERATION CASES IN NONALLERGIC DISEASES

	POLYPS	POLYPOID DEGENERATION
Total cases	14	5
Found to have asthma	12	1
Found to have vasomotor rhinitis	1	1
Found to have hay fever	0	1
Cases with neither personal nor familial allergy	1 (proved on section to be carcinoma)	2 (1 had 4% eosinophiles) (1 had red mucosa in nose and tracheobronchial tree)

We next sought to investigate all of those patients in the nonallergic disease group, who were found to have polyps, for a possible allergic factor. In those cases which we were unable to study directly, we searched the hospital record for evidence of possible allergy. Of the 14 individuals with nasal polyps, in one a supposed polyp proved on section to be carcinoma. Of the other 13 polyp cases, 10 had bronchial asthma, one had bronchial asthma and vasomotor rhinitis, and one had vasomotor rhinitis alone. The remaining patient, a boy of seventeen years, with extensive bronchiectasis, gave a pronounced family history of asthma, vasomotor rhinitis and urticaria. At the age of eight years he had had symptoms that had led an experienced pediatrician to make a diagnosis of bronchial asthma. When recently seen by us, the patient gave positive skin tests to house dust and feathers. Of the five patients with "polypoid degeneration of the mucosa," one had bronchial asthma, another had vasomotor rhinitis and a third had hay fever. The remaining two patients we have been unable to trace. Their records were silent as to both personal and familial allergy, but contained a little evidence that might be suggestive. One patient had an eosinophile count of 4 per cent. The other, a patient with bronchiectasis, was described as having a red, congested lesion, not only in the nose but also in the tracheobronchial tree as determined by bronchoscopy.

A series of similar cases will be presented in detail in an article now in preparation.

DISCUSSION

It would seem, then, that probably all patients with typical nasal mucous polyps are of the allergic or hypersensitive constitution. It would seem, too, that infection alone, i.e., infection in the absence of an allergic constitution on the part of the patient, cannot lead to the formation of typical nasal mucous polyps. The next question which arises is: how is this allergic factor active?

A significant fact is this: the incidence of mucous polyps is greatest in the perennial and protracted cases of allergic disease. This would suggest the possibility of the *prolonged* action of atopens on the mucosa as a factor in the production of polyps. What to us seems even more important, is that polyps, like sinus disease, are more common in those allergic states which are perennial and therefore overlap with those seasons of the year in which respiratory infections are prevalent. Furthermore, we have the clinical impression from our allergist colleagues who work in tropical and subtropical fields, that polyps and sinus disease are not so frequent in their asthmatic patients as they are with us in Philadelphia. We therefore believe that bacteria probably play a part in the etiology of many (most?) cases of mucous polyps.

What is the rôle, then, of the bacteria? In the past, comparatively few workers in the field of allergy have been willing to subscribe to the concept of hypersensitiveness to bacterial protein. Certain it is that it has been impossible to trace an exact parallel immunologically between atopy and so-called bacterial hypersensitiveness. On closer study, however, it would seem that the differences between the two states are rather matters of degree than of kind. Some of those who at first opposed the concept of bacterial allergy have been more recently inclined to give it serious consideration. Thus Cooke[45] has been impressed by the fact that in the so-called infectious type of asthma, a condition formerly considered nonallergic, there is just as pronounced a history of familial hypersensitiveness as in true atopy. Thomas and Touart have long held to the view that true bacterial hypersensitiveness plays an important part in clinical allergy and have recently restated their views and summarized the literature up to the present.[46] This year at the meeting of the Society for the Study of Asthma and Allied Conditions, Grove and Cooke[47] presented evidence from which they concluded that the hyperplastic changes in the nasal and sinus mucosa of asthmatic individuals are an expression of bacterial hypersensitiveness. While more evidence is necessary, we feel that it is but a step from this position to the assumption that bacterial allergy explains the mode of action of bacteria in the production of mucous polyps.

It is our belief that in the majority of cases the protracted action of allergens produces a chronically swollen mucosa (an allergic swelling). This state, continued into the seasons of the year when respira-

tory infections are common, prepares the way for bacterial hypersensitivity. In a minority of cases there occurs first an infection with an infectious swelling of the mucosa, and eventually if the patient is of allergic strain, there can supervene a true bacterial hypersensitiveness. This latter will continue to keep the mucosa in a swollen state, but the swelling is then no longer inflammatory (red, congested) but allergic (pale, edematous, hyperplastic). The edematous mucous polyp is therefore the ultimate degree of allergic change in the mucosa.

TREATMENT OF MUCOUS POLYPS

If it be true that allergy is a constant factor in the etiology of mucous polyps, then a search for the allergic factor becomes a prime requisite in the study of all cases of mucous polyps.

The treatment of polyps must then include attention to possible atopic hypersensitiveness as well as to the bacterial factor. Obviously, the simple avoidance of an inhaled allergen to which the patient may be sensitive will not be sufficient as a rule to cause the polyps to disappear, although in a few instances we have seen this occur—certainly the early degrees of polypoid change can regress on avoidance of the offending allergen. But the avoidance of the allergen is essential to prevent the recurrence of the polyps after their operative removal. Of course, the adequate drainage of infected sinuses, the use of bacterial vaccines, and proper local treatment follow the usual principles in such cases. In short, we would extend to the treatment of all mucous polyps those measures which allergists have long recognized to be applicable in their asthma and vasomotor rhinitis patients who present this complication.

CONCLUSIONS

1. Mucous polyps are extremely common in allergic conditions of the respiratory tract.

2. In patients with presenting symptoms of nonallergic diseases of the respiratory tract, mucous polyps are comparatively rare, even in the presence of extensive and chronic sinus infection.

3. In our experience, all patients with mucous polyps have been found to have a personal history of allergy, a history which others have usually overlooked in those instances where the patient's presenting symptoms were those of a nonallergic disease (e.g., tuberculosis, arthritis, etc.).

4. It is significant that mucous polyps occur particularly in those types of respiratory allergy that are protracted and perennial, suggesting that a bacterial factor is present.

5. The rôle of bacteria in the production of polyps is uncertain; it is suggested that true hypersensitiveness to bacteria is the usual mechanism.

6. The finding of mucous polyps in a patient warrants the assumption that the individual is of allergic strain and that he should therefore be studied completely from the standpoint of clinical hypersensitiveness.

7. The treatment of patients with mucous polyps must include attention to the allergic factor; the failure to reckon with this factor is the prime cause for the postoperative recurrence of the condition.

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FURTHER OBSERVATIONS ON THE NATURE OF ALLERGY*†

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THREE years ago, one of us[1] discussed The Nature of Allergy, calling attention to several clinical characteristics which were common to patients with asthma and hay fever. These allergic individuals were different from normal persons. It was pointed out that all gradations between the two groups existed and that, therefore, the difference was more of degree than of kind. Nevertheless, the phenomena of allergy are so striking as to demand investigations of the reason why certain persons have a marked increase in the capacity to develop sensitiveness to foreign substances and in the other capacity of reacting to these same substances. The phenomena concerned in the process are numerous. Some of them like heredity are concerned with the fundamental background of the allergy, while others represent simply the effects of that allergy after its establishment. The fact that it is often difficult to distinguish between the causes and the effects of the process often leads to confusion in the interpretation of results.

In searching for the cause of allergy, one thinks of endocrine disturbances and of dietary defects. So far, however, we have little real knowledge to help us with either of these two possibilities.

The effects of the fundamental cause are a little more tangible. The allergic reaction depends probably upon the presence of specific antibodies which are more numerous on the cell surfaces than free in the circulating blood. The process appears to be a disturbance of the immune mechanism, and it is quite natural to suppose that immune responses in general are different in allergy than in normal persons.

Second, the symptoms of allergy are quite the same regardless of the specific cause, whether this be a pollen, a household dust, or a food. Evidently, the reaction elicited by any one of these foreign substances leads to the same end product which, from the work of Sir Thomas Lewis, we can suspect to be histamine. The immune responses and the reaction of the individual to histamine would, therefore, be reasonable subjects for investigation.

The development of agglutinins following typhoid vaccine was selected as a typical immune response, although its limitations as indi-

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†From the Medical Services and the Anaphylaxis Clinic of the Massachusetts General Hospital, Boston, Mass.

cating any fundamental resistance of the body to infection are well recognized. A group of patients with asthma has been compared with a group of normal nurses in their response to four small subcutaneous doses of triple typhoid vaccine. The patients with asthma were selected from the intrinsic group in whom it was not possible to de-

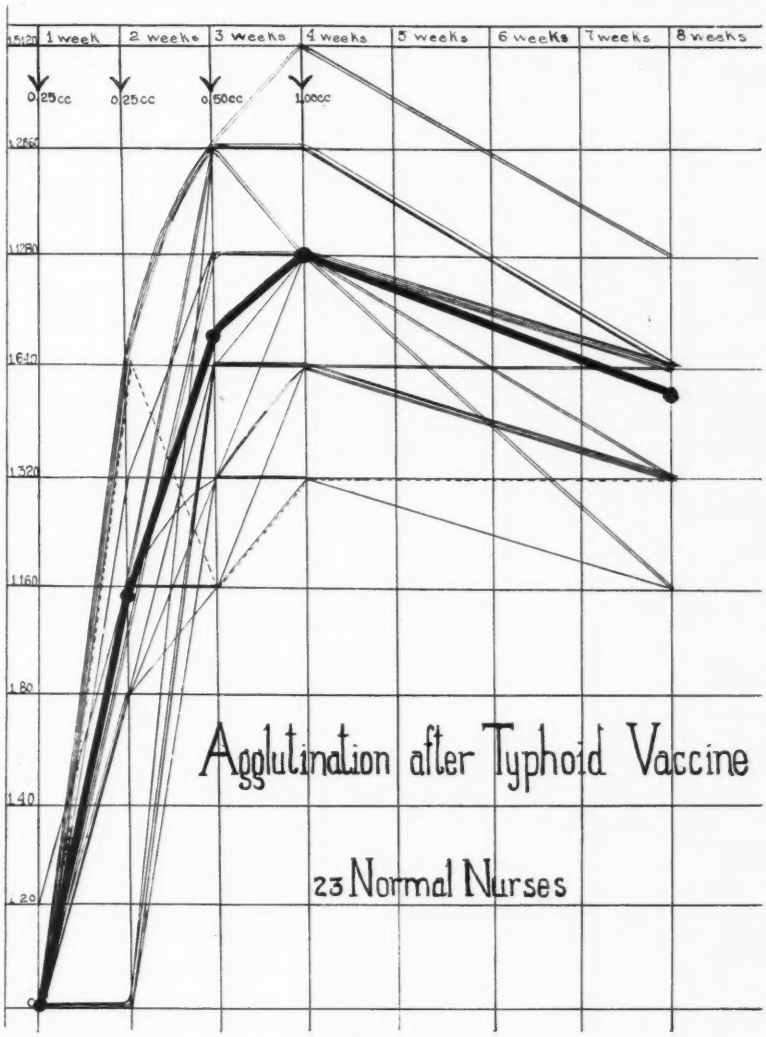

Chart 1.

fine any specific cause for the asthma in dust or food outside the body. In all of them, the asthma appeared to be of bacterial origin. The ages varied from twenty to fifty years, and the duration of the asthma varied from a few to many years. Patients with any suggestion of heart disease or of chronic bronchitis were excluded. The nurses were all young girls who were receiving their typhoid vaccine doses preliminary to the start of their training course. In both groups, the

technic was the same. The vaccine used was the regular Massachusetts State Board of Health triple typhoid vaccine, containing in each cubic centimeter 1,000,000,000 typhoid and 750,000,000 each of paratyphoid A and B, a total of 2,500,000,000 organisms per cubic centimeter.

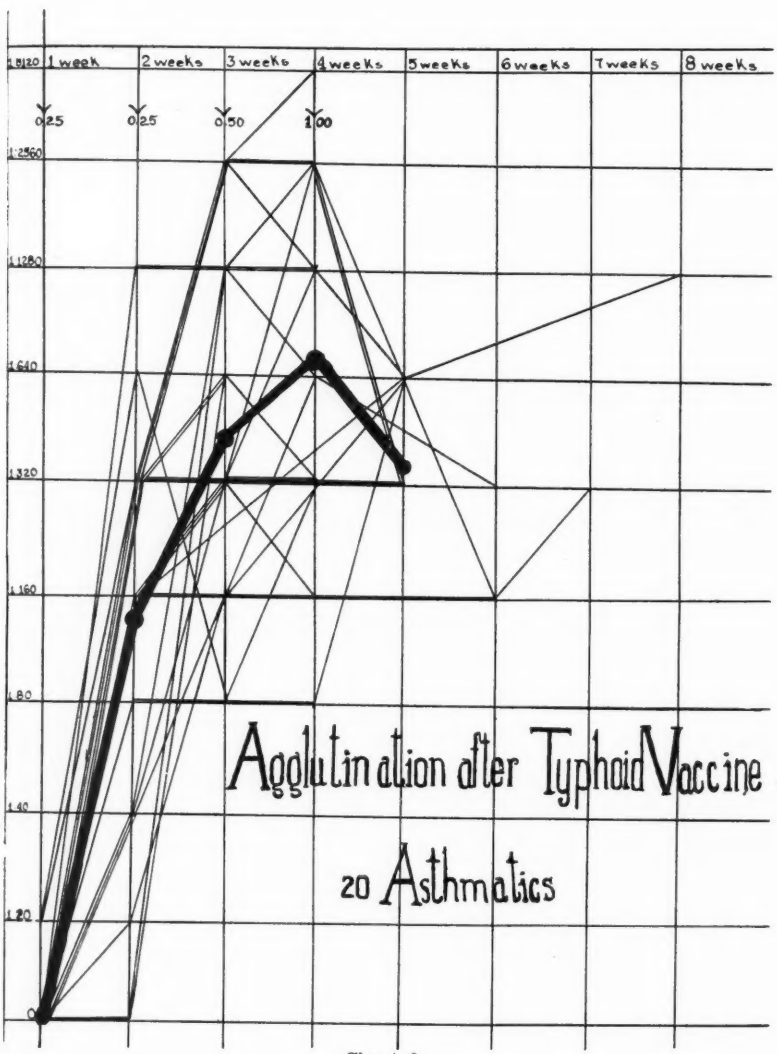

Chart 2.

Each patient and each nurse received four doses of vaccine injected subcutaneously at weekly intervals, the sequence in each case being 0.25 c.c., 0.25 c.c., 0.50 c.c, and 1.00 c.c. Blood was drawn at the time of injecting each dose and dilutions of serum from it from 1:20 to 1:5,120 were titrated against fixed amounts of the antigen which consisted simply of the same typhoid vaccine which had been used for treatment. The figures on the chart show the actual dilution of the

serum after the antigen was added. Incubation was carried out for two hours at 37.5° C. in a water-bath, and then overnight in the ice-box. The readings were made in twenty-four hours. A prezone was encountered in some cases, more often in the asthmatic patients than in the nurses.

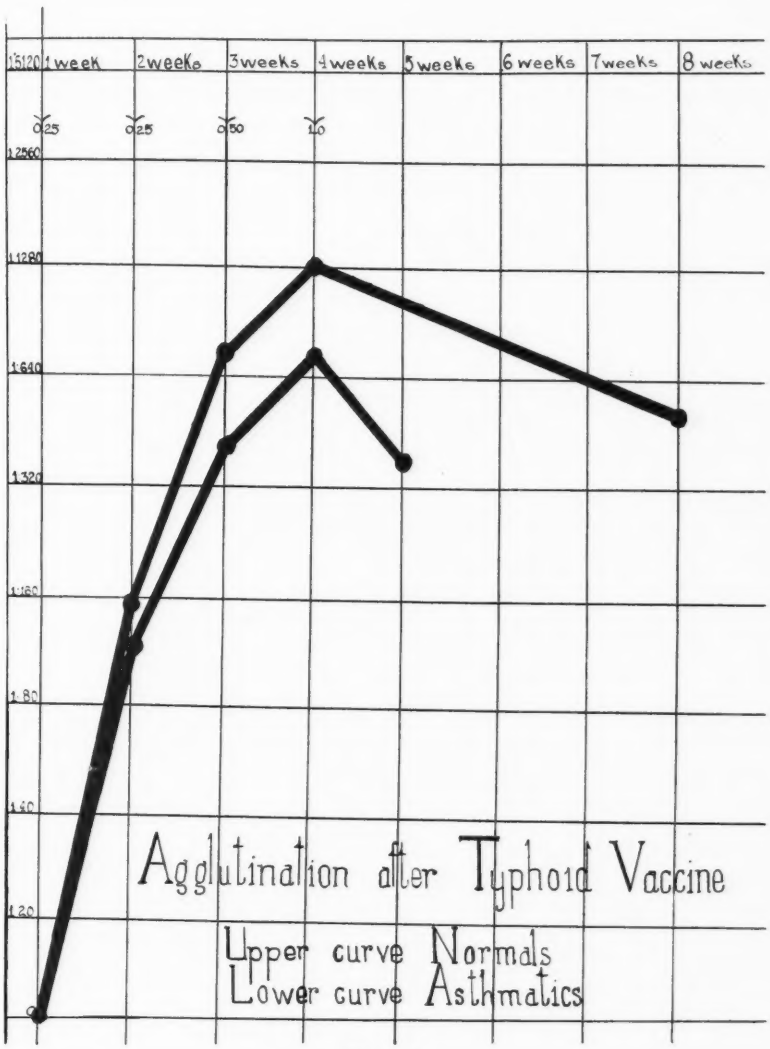

Chart 3.

The results are shown in the accompanying charts. It was observed that among the nurses, the response is relatively uniform. The reaction of one nurse is quite like that of another. A titer of 1:1280 is reached at the time of the fourth dose and stays at a high level for at least eight weeks. In the asthmatic individuals, however, the variation between individual patients is much more marked. This is probably due to the differences in age, sex, and types among the patients. It

is proper to ask whether these differences in the immune response can be correlated in any way with the local reactions from the vaccine doses or with the clinical results of the vaccine treatment. Investigation of this point has, however, failed to show any such correlation because among the patients with a high agglutinin titer, some have done well and some have done badly, and on the other hand, some have had large local reactions and others have had small local reactions following the individual doses. The comparison between the average agglutinin response of the asthmatic and the normal individuals is shown in Chart 3. The curves show clearly that the immune response in asthma is a little lower than the normal; the difference, however, is not great and is merely in the degree of reaction.

The agglutination of other organisms by asthmatic serums was also studied with reference to the agglutination of hemolytic streptococci by the serum of patients with arthritis. Table I shows the results.

TABLE I

AGGLUTINATION TESTS

	STAPH.	HEM.	NONHEM.
23 Nurses	0	0	0
6 Arthritis patients	0	3*	1*
22 Asthma patients	0	1*	1*

* = Positive agglutination.

The *Staphylococcus aureus* was studied first, since it is such a common finding in cultures of the nose and throat in asthma. Never, however, did we observe the presence of agglutinins to staphylococci in a large number of asthmatic serums. The hemolytic streptococcus was investigated. Four strains obtained from routine throat cultures in the hospital laboratory were observed for their ability to grow smoothly in the horse serum medium described by Mueller and Klise.[2] Among the four organisms, one was satisfactory and this was titrated against 60 different serums from 50 different persons. The 23 nurses were all negative. The 6 arthritic patients gave 3 positive results and the 22 asthmatic patients were all negative except for one interesting patient who suffered from both asthma and arthritis. She alone among the asthmatic patients agglutinated the hemolytic streptococcus.

These agglutinations were well marked and showed definite precipitates in the bottom of the tube with perfectly clear fluid above. In only five instances, however, were reactions observed with dilutions as high as 1:320. Nonhemolytic streptococci also obtained from routine throat cultures were studied by the same method. Of three organisms, only one gave a satisfactory and smooth suspension, and this was titrated against serums from the same patients. The 23 nurses were all negative. The six patients with arthritis were likewise negative

except for one and she was the same patient with both arthritis and asthma whose serum agglutinated the hemolytic streptococcus. The other asthmatic patients showed no agglutinins at all to the non-hemolytic streptococcus. This evidence indicates, therefore, that the serums of asthmatic patients do not contain peculiar properties of agglutinating the suspensions of certain bacteria as the serums of patients with arthritis do.

The response to histamine was studied by means of intracutaneous tests with varying dilutions of histamine. The Burroughs and Welcome product called "ergamine acid phosphate" was used in this work, and dilutions of the crystals were made up in carbolized salt solution. The intracutaneous injection of a solution of histamine causes an immediate wheal and erythema (urticarial reaction) which appears in twenty minutes. The tests were, therefore, read in twenty minutes. Preliminary study showed that such positive skin reactions first appeared with dilutions of 1:100,000 and 1:10,000,000 and so, for our routine tests, three dilutions—1:100,000, 1:1,000,000 and 1:10,000,000—were used. A total of 85 patients with asthma were tested intracutaneously with histamine, and the observations were controlled by similar tests on 23 normal nurses. Chart 4 represents a summary of the results obtained. In most of the nurses and the patients, the average reaction consisted of a definite wheal and erythema to the 1:100,000 dilution with or without a slight response to the 1:1,000,000 dilution, but definite reactions to the 1:10,000,000 were lacking. Such average reactions occurred among 91 per cent of the nurses and 83 per cent of the asthmatic patients, but the chart shows that on the whole the response of the asthmatic patients was a little larger than the response of the normal nurses. On the other hand, responses larger than average so that definite wheals were obtained with the 1:10,000,000 dilution were observed in 8 per cent of the nurses and 17 per cent of the asthmatic patients. The difference between the two groups is definite perhaps, but it is only slight and it appears only in case the general average among a fair number of individuals is studied. The positive findings, however, fit in with the observations of Soma Weiss and his associates[3] that patients with asthma react to the intravenous doses of small amounts of histamine in a way quite different from normal individuals and that these reactions are induced by small quantities of the drug.

In the meantime and when most of our observations were completed, McConnell[4] described her own similar study on a series of patients in H. L. Alexander's clinic. McConnell measured very accurately the size of the wheal produced by precise doses of the 1:2,000 dilution of histamine acid phosphate, and she found that in the normal person the wheal varies between 1.2 and 1.7 sq. cm.; that in allergic persons between attacks the wheals are smaller (0.9 sq. cm.), and

that even during attacks, they are still within normal size (1.4 sq. cm.). Our own experience has always been that the response to diminishing dilutions gives more useful information than the exact size of the

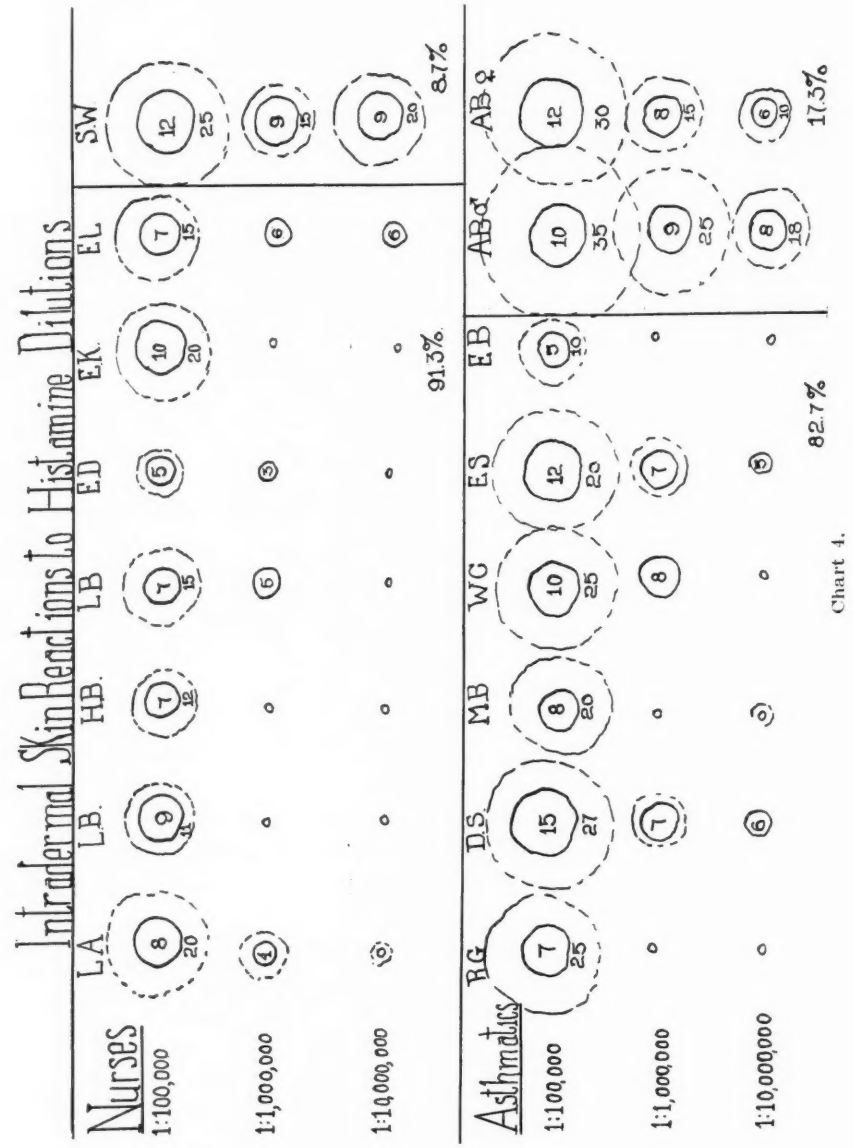

Chart 4.

wheal resulting from any one dose, and we, therefore, maintain that asthmatic individuals are a little more sensitive.

Acting on the theory that the symptoms in asthma are caused by histamine or at least by a histamine-like substance and that the tolerance to this substance is low, we tried to treat our patients with consecutive doses of histamine. Local reactions to this treatment were

likewise quite marked, and it seemed impossible to raise the dose above a certain level without increasing the size of this local reaction to an undue extent. The tolerance to histamine could not be increased by treatment. Although only about 10 cases were studied in this way, the clinical results of this treatment with histamine were unsatisfactory. These observations show that patients with asthma give a larger skin reaction to histamine than do normal individuals; that they are slightly more sensitive to histamine than normal but that the difference is not very great.

SUMMARY

1. The development of typhoid agglutinins was studied in a series of 23 normal nurses and in 20 patients with asthma.

2. The resulting curves show that the agglutinin response in asthma is slightly lower than normal.

3. The search for agglutinins in asthmatic serums for such other organisms as *Staphylococcus aureus,* hemolytic streptococci, and nonhemolytic streptococci gave negative results in all except one patient who had arthritis at the same time with her asthma.

4. Intradermal skin reactions to histamine dilutions were slightly larger among 85 asthmatic patients than among 23 nurses, but the differences were small, and the results seem to indicate that asthmatic patients are slightly more sensitive to histamine than normal.

5. Treatment with histamine did not help in the few patients studied.

6. The differences between patients with asthma and normal persons in their responses to typhoid vaccine and in their reactions to histamine are small.

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HYPERSENSITIVENESS TO ACETYL SALICYLIC ACID EXPRESSED BY AN ANGINA PECTORIS SYNDROME WITH AND WITHOUT URTICARIA*

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HYPERSENSITIVITY to acetyl salicylic acid is not uncommon. Congestion of the nose, edema of the eyelids, constriction and edema of the throat with dysphagia, and angioneurotic edema are some of its manifestations. (Hanzlik.[1]) Cooke[2] has described coryza, bronchial asthma with urticaria, angioneurotic edema, frequent gastrointestinal manifestations with pain, vomiting and diarrhea, and in one case cardiac collapse. The angina pectoris syndrome has not been mentioned as an evidence of hypersensitivity to acetyl salicylic acid.

The following case reports are of interest because these patients, after the ingestion of acetyl salicylic acid and at no other time, developed an angina pectoris syndrome. In one patient there was an accompanying urticaria with other possible allergic manifestations and temporary electrocardiographic changes, in another case an accompanying urticaria, and in the third case no accompanying manifestations.

CASE 1.—S. K. Female, thirty-eight years old, white, married, U. S. Family history negative for degenerative or allergic disease.

Past History: Usual childhood diseases; typhoid at six years. 1926—Cholecystotomy. 1927—Mucous colitis, controlled by diet and medication; no organic gastrointestinal disorders. Shortly after this a hypertension was found. In 1929 she noticed a feeling of heaviness and pressure in the chest after taking acetyl salicylic acid for headaches or colds. In 1930, after taking ten grains of the drug she suffered an attack similar to the one described below. She made an uneventful recovery. In December, 1932, she was given ten grains of acetyl salicylic acid, in powder form, for a cold without her knowledge. One-half hour later she experienced a tingling sensation under the skin which lasted about ten minutes. This was followed by a severe vise-like pain in the chest, radiating to both arms and to the back and also to the upper abdomen; she had a sense of impending doom and was almost in collapse. A tentative diagnosis of a coronary occlusion was made. The blood pressure had dropped from 180 mm. systolic to 100

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mm. Within one hour all the symptoms had disappeared; no temperature reactions were noted, and blood studies were negative the following days.

The patient was certain that she had been given acetyl salicylic acid, for she said the attack was similar to the ones she had previously experienced after taking the drug.

Physical Examination: January, 1933. Heart normal in size and shape; short systolic murmur at the apex, not impairing the quality of $S\text{-}_1$; $A\text{-}_2$ accentuated. Blood pressure 190/100. Some obliteration of the smaller retinal vessels. Brachial pulsations were visible and the radial vessels were slightly thickened. No evidence of kidney dysfunction. The electrocardiogram showed a prominent Q-wave in the third lead. Patch tests by Dr. Lieberman were negative.

Diagnosis: Essential hypertension; retinal and radial vessel sclerosis; angina pectoris syndrome as an expression of a hypersensitivity to acetyl salicylic acid.

CASE 2.—M. M. Female, married, aged thirty-five years, colored, U. S.

Family History: Mother has a hypertension. One brother and four sisters all react by an urticaria to the ingestion of strawberries and fish; one sister has a bronchial asthma; and one sister's child has an idiosyncrasy to acetyl salicylic acid, expressed by urticaria.

Past History: As long as she remembers she would develop a rash on eating shell food or strawberries. In 1923 she developed a cough with asthmatic wheezing which has persisted up to the present time. In 1929, after taking five grains of acetyl salicylic acid, she developed severe pressure pains in her chest with weakness and a rash. She also complained of an inability to swallow; she felt a lump at the lower sternal level (esophageal spasm). The following day she felt well. In 1930 she again developed an attack after taking acetyl salicylic acid; this time, however, she also had a tachycardia which lasted several hours. In 1932, four hours after she had taken ten grains of acetyl salicylic acid, she developed a giant urticaria, followed by severe constricting pain in her chest with radiation to her back and arms; she showed definite signs of shock; pulse was rapid and thready, and blood pressure had dropped. Several hours later she felt well.

Physical Examination: January, 1933. Well-nourished female, weight 190 lb. Sibilant and sonorous râles in the chest. Blood pressure 130/95. Temporal vessels tortuous; retinal vessels sclerosed; radial vessels slightly palpable. Heart normal in size and shape; $A\text{-}_2$ accentuated; no murmurs.

Fluoroscopy showed the aortic knob rather prominent; the aorta seemed rigid and tortuous. Electrocardiogram indicated a left axis deviation and slight slurring of the main deflections in the second and third leads.

Patch tests were negative; no other testing was allowed.

Diagnosis: Presenile retinal, radial and aortic sclerosis; chronic bronchitis; hypersensitivity to certain foodstuffs and acetyl salicylic acid.

CASE 3.—E. S. Male, forty-four years of age, Austria.

Family History: Father died at seventy-five years, cerebral hemorrhage; mother is well; no brothers and no sisters; no familial history of atopy.

Past History: Does not remember diseases of childhood. Kidney colic in 1926; no stone passed; no subsequent attacks. Was well up to September, 1932. At that time he developed a headache, for which he took ten grains of acetyl salicylic acid—a drug he had previously taken without untoward results. Several hours later he experienced a choking sensation, made worse on walking. He, however, kept on to his destination and upon arrival there had severe viselike pains in the chest with difficulty in breathing, became covered with cold perspiration, vomited, and had pain in the upper abdomen. His face and arms were red and covered with large blotches. His vision became blurred. A diagnosis of a coronary attack was made. On December 1, 1932, he had a similar attack, again after taking acetyl salicylic acid. He came to the clinic of the Jewish Hospital of Brooklyn for relief.

Physical Examination: Well-nourished sthenic type male; lungs show evidences of chronic bronchitis and emphysema. Blood pressure 150/90. Left ventricle slightly rounded; A_2 accentuated; regular sinus rhythm. Abdomen negative. Left inguinal hernia. No evidences of kidney dysfunction.

Electrocardiogram showed a regular sinus rhythm, ventricular rate 100; the P-R interval in the second lead was 0.17 second. All main deflections slurred. Left axis deviation.

Patch tests as well as skin tests were negative.

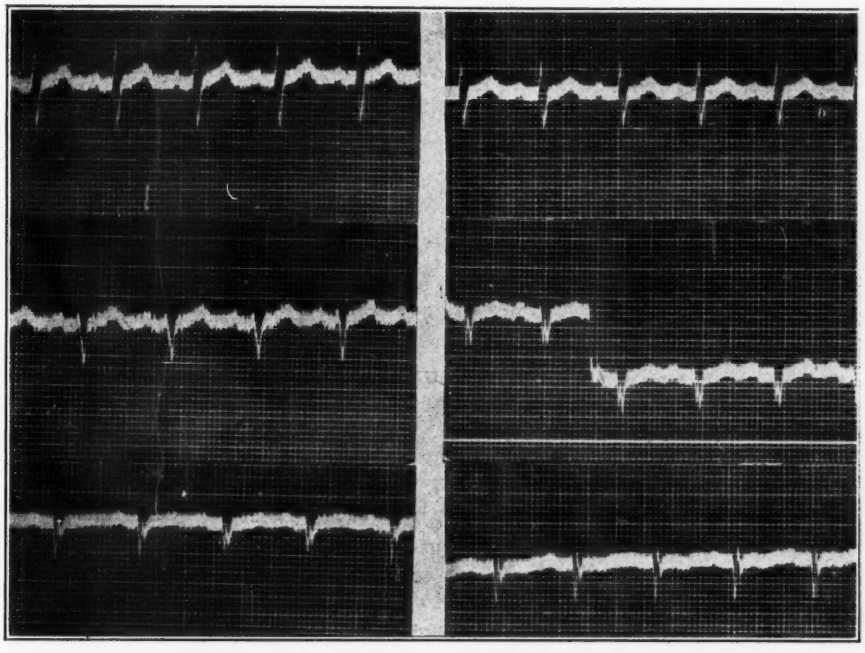
Diagnosis: Early essential hypertension; cardiac hypertrophy; coronary vessel sclerosis; hypersensitivity to acetyl salicylic acid.

Attacks were always produced by administration of acetyl salicylic acid. They would start three and a half hours after its ingestion and would begin with a feeling of heaviness in his chest, later developing into severe viselike pain and with a feeling of numbness in both arms; his face, arms and chest become flushed, and a marked urticaria would appear.

On December 31, 1932, patient was observed at the clinic before and after he was given ten grains of acetyl salicylic acid. The data reported in Table I were obtained.

The significant findings were: (1) Increase in the eosinophile count from 2 per cent before the administration of the drug to 4 per cent to

5 per cent about five hours later (4:30 P.M.). (2) Gradual decrease in blood pressure from 130/90 before the administration of the drug to 100/76 (3:30 P.M.). (3) Cardiac rate varied from 84 to 100 (3:30 P.M.). At 4:20 P.M. cardiac rate was 90 and after the administration of 10 mm. of adrenalin at 4:25 P.M. the cardiac rate dropped to 73. At 4:40 P.M. rate was 92; and at 4:55 P.M., after 10 mm. of adrenalin it dropped to 74. (4) Pain in chest and urticaria first appeared at 2:15 P.M. and was



A *B*

Fig. 1.—Case 3. Electrocardiograms taken (*A*) before and (*B*) during attack, showing the changes particularly in the second lead; marked notching of the main deflection; prolongation of the P-R interval. The main deflection in the third lead is deeper and is inverted.

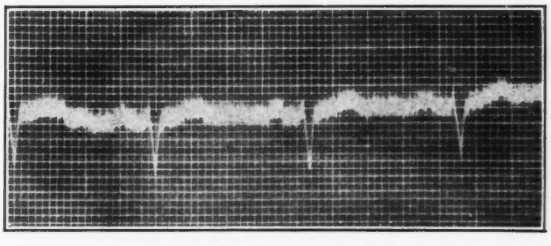


Fig. 2.—Case 3. This is the second lead taken one or two minutes after the administration of 10 mm. of 1:1000 adrenalin. (4:55 P.M.) Immediately preceding this, the ventricular rate had been 92.

marked at 3:30 P.M. This persisted and increased until 4:20 P.M. There seemed to be a slight diminution of symptoms after adrenalin; they however, wore off gradually. At home at 7:00 P.M. patient had a severe attack of angina, urticaria and collapse; this occurred about three

TABLE I

TIME	DRUG	BLOOD PRESSURE	RATE	EOSINOPHILES	ELECTROCARDIOGRAM	SYMPTOMS
11:45 A.M.		130/90	92	2%	RSR. Slurring of all main deflections. T_1, T_2, T_3 upright. S_2 main deflection. P-R interval 0.17 second. L.A.D. (Fig. 1*A*.)	No symptoms.
11:50	Acetyl Sal. Acid gr. X.					
12:50 P.M.		130/88	88		Same.	
1:50			84	2%	Same.	
2:15						Viselike pressure in chest. Itching of skin. Face flushed. Urticaria on forehead, chest and back.
2:50	Acetyl Sal. Acid gr. V.	120/80	88	3%	Same.	
3:30		100/76	100	3%	EKG changes. P-R interval 0.2 second. T_3 inverted R_2 widely split. S_3 plus. T_1 slightly lower. (Fig. 1*B*.)	Constricting viselike pain in chest, radiating to both arms. Itching marked. Erythema and urticaria increased.
4:20			90		Changes disappeared. Return back to previous electrocardiogram.	Pressure pain in chest radiating to both arms. Marked weakness. Urticaria marked.
4:25	Adrenalin 1:1000; M. X.					
4:30		110/84	73	4-5%	Same; except slower rate.	Urticaria definitely diminished. Pressure in chest persists. Hypersensitive over left chest.
4:40			92		Same; increase in rate.	Symptoms letting up.
4:50	Adrenalin 1:1000; M. X.					
4:55		118/90	74		Same; rate 74. (Fig. 2.)	Chest pain almost gone. Patient feels weak. Urticaria almost gone.

Patient refused to stay in the hospital any longer.

7:00 P.M.—At home. Very severe pain in chest, radiation to left shoulder and arm; difficulty in breathing; rapid, thready pulse; severe urticaria; collapsed. Hypodermic of MS. given. The following morning he complained of soreness in chest; pulse of good quality. Blood pressure 140/90; temperature and blood counts normal. No evidence of a myomalacia cordis.

and a half hours after the administration of another five grains of acetyl salicylic acid at 2:50 P.M. (5) At 3:30 P.M. electrocardiographic changes (Fig. 1) (during attack) were noted. Prolongation of the P-R interval in the second lead. Distinct notching of $S\text{-}_2$. $S\text{-}_3$ increased; $T\text{-}_3$ inverted. At 4:20 P.M. these electrocardiographic changes had disappeared. Electrocardiographic abnormalities were not found in every attack.

DISCUSSION

In all three cases a certain time after the ingestion of acetyl salicylic acid—in Case 1 one-half hour; in Cases 2 and 3 approximately three and a half hours—a very definite angina pectoris syndrome developed with definite pain characteristics, localization and radiation. These attacks lasted somewhat longer than the ordinary spastic anginal attacks. They were accompanied by drop in blood pressure, increase in cardiac rate and symptoms of collapse; they simulated attacks of coronary thrombosis. None of the signs of myomalacia cordis, i.e., leucocytosis, temperature rise, sedimentation rate disturbances or subsequent symptomatology, were present. In Case 3 definite changes in the electrocardiogram during the attack were noted; these changes were temporary. Bearing these data in mind, it would seem that the findings were due to a temporary heart muscle involvement with no resultant myomalacia, possibly similar to the temporary exudative states seen in those organs which usually manifest evidences of hypersensitivity.

In Case 1 other evidences of anaphylaxis or allergy were not present. In Case 2 a giant urticaria appeared at the same time as the angina pectoris syndrome. This patient had a definite familial and personal history of hypersensitivity to other substances. In Case 3 we found an accompanying urticaria, increase in eosinophile count, parasympathetic instead of sympathetic response to adrenalin, findings at least suggestive of the possible allergic nature of these phenomena.

The anginal syndrome and the other manifestations of hypersensitivity were accompanying symptoms, both occurring at a rather definite time after the ingestion of the drug in each individual case. This point is noted in Case 3. The initial ten grains of acetyl salicylic acid were given at 11:50 A.M. and at 2:15 P.M. slight symptoms began to appear; at 3:30 P.M. the symptoms were rather pronounced. At 2:50 P.M., however, another five grains of the drug was given, and at 7:00 P.M., about four hours after the administration of the second five grains, patient was again in the throes of a very severe attack. There seems to be, therefore, a more or less fixed relationship between the administration of the drug and the time of the appearance of symptoms in each case.

All three patients have more or less definite symptoms and signs of cardiovascular degenerative disease. In Case 1 hypertension, A_{-2} accentuated, retinal vessel sclerosis, thickening of the radial vessels; prominent Q-wave in the electrocardiogram. In Case 2 tortuous temporal vessels, retinal vessel sclerosis, accentuated A_{-2}, slightly palpable radial vessels, tortuous and rigid aorta; and slurring of the main deflections in the second and third leads with a left axis deviation. In Case 3 tendency to a hypertension, A_{-2} accentuated, rounding of the left ventricle; and slurring of the main deflections in all leads, with a left axis deviation.

We believe, therefore, that the cardiovascular manifestations, whether their nature be allergic (Cooke,[2] Alexander,[3]) or anaphylactic (Wolff-Eisner[4]), or neither (Hanzlik[1]), are an evidence of hypersensitivity to acetyl salicylic acid, expressed in part by the cardiovascular system because of the preexisting disease of that system. It seems that the cardiovascular system in health usually takes little part in the syndrome of hypersensitivity. When diseased, however, it may wholly (Case 1) or in part, account for this syndrome. We have in a previous report described cardiovascular symptoms in response to ragweed pollen sensitivity, the usual hay fever and asthmatic manifestations being replaced by repeated anginal attacks (Shookhoff and Lieberman[5]).

SUMMARY

Three cases of hypersensitivity to acetyl salicylic acid expressed by an angina pectoris syndrome—in two cases accompanied by urticaria—are reported. None of the characteristic signs of a myomalacia cordis were present. A study of one case showed definite allergic manifestations and definite electrocardiographic changes in the attack produced by the ingestion of acetyl salicylic acid. The electrocardiographic changes disappeared before the subsidence of the reaction. This syndrome in this individual was produced with every administration of acetyl salicylic acid and was, to some degree, controlled by the administration of adrenalin. There were evidences of preexisting cardiovascular disease in all three cases.

NOTE.—We wish to thank Miss Vaughan, our technician, for her assistance.

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ANGINA PECTORIS SYNDROME, ACTIVATED BY RAGWEED SENSITIVITY IN A PATIENT WITH CORONARY VESSEL SCLEROSIS: CASE REPORT*

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SEVERAL articles have appeared in the literature on the relationship between the angina pectoris syndrome and allergy. Some writers believe that hypersensitivity to certain substances, particularly foods, may be the direct cause of coronary thrombosis;[1] others believe that the allergic state may be the exciting factor in the causation of an anginal syndrome in individuals who apparently have no cardiovascular disease;[2] and still others deny there are any cardiovascular manifestations of the allergic state. Many authors have attempted to show that the occurrence of extrasystoles, paroxysmal tachycardias,[3, 4] hypertension, etc.,[5, 6] may be evidences of the activity of an allergic disorder. Koessler, Lewis and Walker[7] have shown experimentally that filtrates from bacterial growths especially prepared, contain substances that cause arterial constriction in vitro and a rise in blood pressure in vivo. Kern[8] stated, "That allergic manifestations may be precipitating factors in bringing about or bringing to the surface an existing subsurface cardiac lesion is obvious, but to insist on a strict etiologic relationship I would say is totally unjustified." Recently Harkavy,[9] in an investigation of a series of patients, all heavy smokers, with coronary arteriosclerosis and the angina pectoris symptom complex with diagnostic electrocardiographic changes, found 36 per cent who gave positive intradermal urticarial reactions to tobacco. He believes[10] that tobacco sensitivity is probably the exciting factor in the production of the angina pectoris syndrome in these individuals.

We feel justified in reporting the following case because of the rather clear causal relationship between frequent and repeated attacks of the angina pectoris syndrome, coming on during the period of ragweed sensitivity, in a patient who gives definite signs and symptoms of both coronary vessel sclerosis and sensitivity to ragweed. Measures instituted to relieve the manifestations of ragweed sensitivity caused the disappearance of the anginal syndrome.

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CASE REPORT

M. R., male, sixty-three years of age, clothing cutter, retired.

Family History: Mother died at forty-five years of asthma; father at sixty-five years, cause unknown. One brother died of coronary vessel disease.

Past and Present History: Was apparently well up to the age of thirty years. He then contracted a cold which persisted for a year, and since then has had frequent colds and repeated attacks of bronchial asthma. At fifty-seven years he developed signs of hay fever in August and September. Skin tests showed a marked sensitivity to ragweed. He was given preseasonal treatment and showed a definite improvement. In 1926, patient began to complain of dizziness, headaches and a pressure sensation in his chest with pain radiating to the back and down the left arm, upon walking a short distance or after excitement. These attacks would subside on resting. In June, 1928, because of a rather severe attack of bronchial asthma which was thought to be cardiac in nature and because of the attacks of angina on effort, patient came for relief.

Physical Examination: A moderately well-nourished individual, weight 119.5 pounds; height 60.75 inches. Eyes, pronounced arcus senilis; normal reaction to light. Eyegrounds showed a sclerosis of the retinal vessels. Radial and temporal vessel walls thickened and tortuous. The dorsalis pedis, right, was not palpable. Blood pressure 200/90 mm. No cardiac enlargement; A_2 accentuated; P_2 normal; heart sounds of good quality; sinus bradycardia. Abdomen negative. No evidence of cardiac insufficiency. The lungs showed signs of emphysema; sibilant and sonorous râles were present throughout.

Electrocardiographic study (Fig. 1 *A*) shows a sinus bradycardia, average ventricular rate 58. No T-wave or R-T interval disturbances. P-R_2 = 0.14 of a second. Left axis deviation.

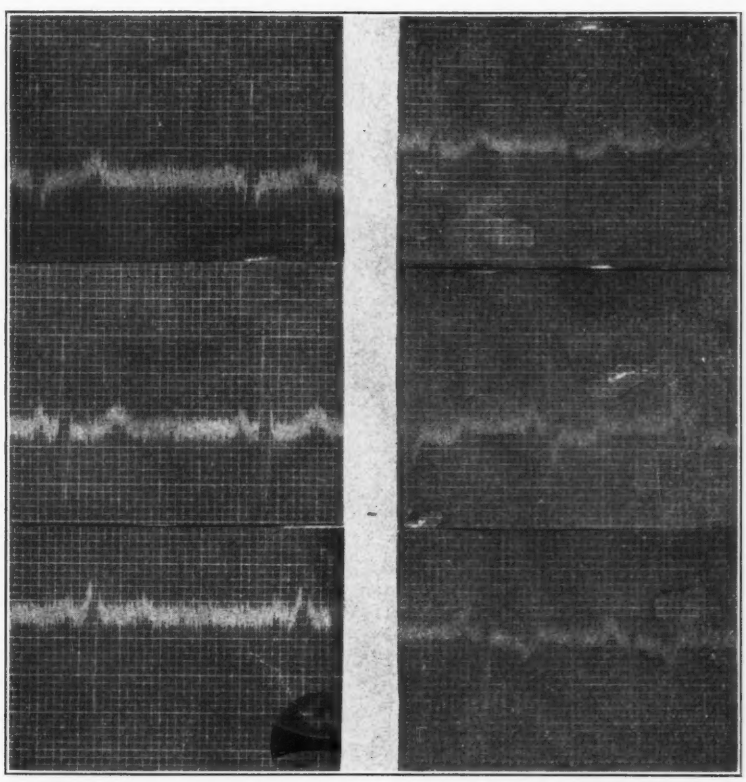
Fluoroscopy: Normal ventricular outline; the aorta appeared tortuous and could be visualized throughout in the second oblique position.

The diagnosis was essential hypertension; generalized arteriosclerosis; chronic bronchitis and emphysema and ragweed sensitivity.

For the following two years patient suffered mild hay fever manifestations in pollen season and the anginal syndrome on effort at all times. In June, 1930, he suffered a coronary occlusion. Drop in blood pressure, leucocytosis, temperature and other classical symptoms of this syndrome were present, together with signs of low grade decompensation. Electrocardiographic study (Fig. 1 *B*) showed inversion of the T-waves in the second and third leads. The patient became partially active after a time and felt as he did before the myocardial

insult, i.e., his blood pressure remained between 145 mm. and 160 mm. Hg systolic.

During the end of the second week of August, 1932, he began to complain of severe attacks of pressure and pain in his chest with radiation to his left arm and back and a feeling of impending doom. He would become pale and at times cyanotic. The attacks would last from five to ten minutes and occurred three or four times a day for the first few days. By the end of the week he was having as many as twenty-five to thirty attacks in twenty-four hours. There were no



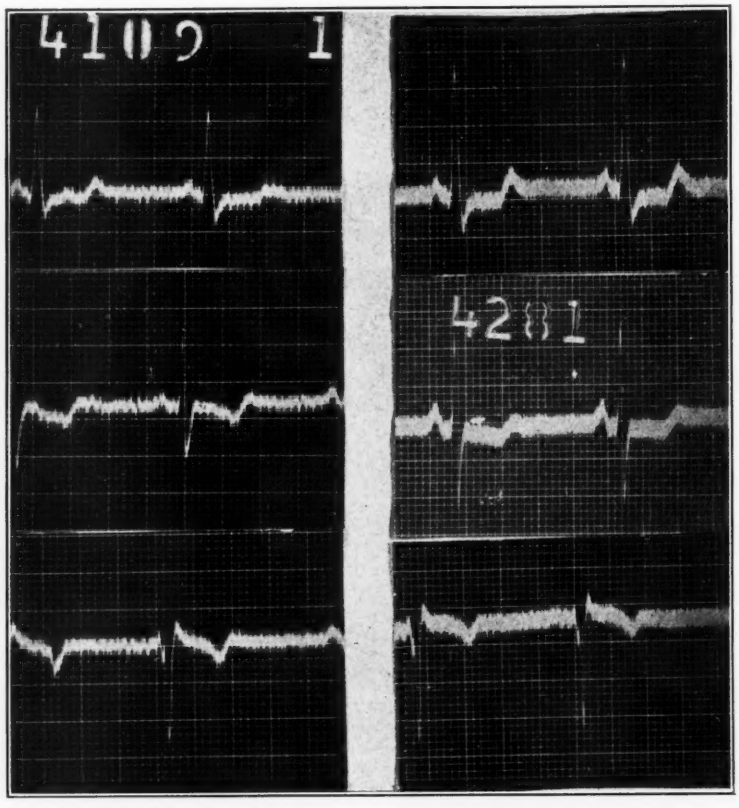
A *B*

Fig. 1.—*A*, electrocardiogram taken June 12, 1928. It shows no T-wave or R-T interval changes; left axis deviation.

B, taken June 30, 1930, shortly after the patient had a coronary occlusion. It shows T-wave changes in the second and third leads.

hay fever or asthmatic manifestations at this time. All the usual medications—xanthin and purin base derivatives, barbituric acid preparations—gave no relief. Papaverin hydrochloride, pantopon, and morphine were impractical because of the large and frequent doses necessary to give some relief. Amyl nitrite inhalations tended to shorten the attacks. In the attacks the blood pressure would go to 200/100 mm., and in between attacks would be between 145-150/95 mm. No temperature reactions were noted.

Ephedrine was then given—8 mm. to 10 mm. of a 3 per cent solution, every three hours—and for the first two or three days the attacks decreased, both in severity and in frequency. However, on the fourth day he seemed to have established a tolerance for this drug, and the attacks again returned to the former number and severity. In view of the possibility that the allergic state was activating the anginal syndrome, we decided to install a pollen filter. Upon its installation the attacks became less severe; in the first twenty-four hours he had only four mild attacks, and in the subsequent twenty-four hours he



A *B*

Fig. 2.—*A*, taken October 14, 1932; and *B*, taken March 22, 1933. These curves show no marked differences and are similar to the curve taken in June, 1930, shortly after the coronary occlusion.

had only two attacks and from that time on to the end of the season the attacks disappeared entirely. The filter was installed on September 4, 1932, at the height of the ragweed season, and was removed about the tenth of October. Patient felt so comfortable in his room that he feared for a time to leave it. He has since had no attacks except those which come on after walking—the attacks that he has had for five or six years. It is interesting to repeat that during the rag-

weed season of 1932, the period of these frequent and severe anginal attacks, he had no hay fever or asthmatic manifestations.

In November, 1932, he gave the following skin reactions: ragweed—0.1 marked; almond—0.05 marked; flaxseed—0.001 moderate; house dust—moderate, plus.

Electrocardiograms (Fig. 2 *A* and *B*) taken in October, 1932, and March, 1933, show no change from the one taken after the patient's coronary occlusion in 1930.

At present the patient feels moderately well and has only occasional slight asthmatic wheezing, with pain in his chest only on more than usual walking.

DISCUSSION

This man presents all the clinical criteria for the diagnosis of an essential hypertension, generalized arteriosclerosis with sclerotic involvement of the coronary vessels. He suffered a definite coronary occlusion in June, 1930. He also presents definite evidence of atopic hypersensitiveness, as shown by attacks of bronchial asthma, seasonal attacks of hay fever, family history and positive skin reactions to ragweed, almond, flaxseed and house dust.

The anginal attacks of August, 1932, differed from previous anginal attacks in that they come on in markedly increased severity and frequency and without relationship to effort, eating or excitement, and only during the ragweed season; they were not relieved by the usual medications and were accompanied by an increase in systolic and diastolic pressures, which dropped to their usual levels between attacks. There were no temperature reactions. These attacks were relieved to some degree by ephedrine and entirely relieved by the installation of a pollen filter.

Apparently no further myocardial damage had resulted during these attacks, since there were no clinical evidences of myomalacia cordis; and the electrocardiographic studies taken in August, 1932, at the height of the attacks, October, 1932, and in March, 1933, do not differ to any great degree from the electrocardiogram taken after the coronary occlusion in June, 1930.

During the anginal attacks of August, 1932, the patient had no asthmatic or hay fever manifestations. It seems to us, therefore, that these attacks were allergic manifestations in the cardiovascular system and were possibly the equivalent of the usual nasal or pulmonary symptomatology. The definite response to treatment by ephedrine until the patient established a tolerance for that drug, and to the removal of the exciting allergic substance by the installation of a pollen filter, goes a great way toward strengthening our concept. Reproduction of the above symptomatology by the administration of ragweed extract would, of course, have definitely proved the case. In

view of the fact, however, that at this time, at least, the shock organ was the cardiovascular system, we were rather timid in following such a procedure. This patient has had ragweed sensitivity for many years; to our knowledge he has had the combination of ragweed sensitivity and coronary vessel sclerosis for almost five years, and still this is the first season in which cardiovascular manifestations apparently superseded the hay fever or pulmonary manifestations. We do not know why this is and we are not at all sure that in subsequent seasons the same manifestations may take place. It will be interesting, however, to note how this patient will react during the next ragweed season.

We are not of the belief that the arteriosclerosis was caused by the allergic disease. It has been shown by several investigators that patients with long-standing bronchial asthma have shown no definite pathologic changes in the pulmonary vessels or in the heart.[11, 12] Alexander[13] has shown the absence of sclerosis in the vessels of the greater circulation in patients with long-standing bronchial asthma. We feel, however, that the allergic state can bring to the fore cardiovascular symptoms in an individual made susceptible by cardiovascular pathologic conditions and that these manifestations may be controlled by the treatment of the allergic state.

SUMMARY

A case is reported of a patient with essential hypertension, generalized arteriosclerosis, coronary vessel sclerosis and who is suffering from a proved allergic state, who presents repeated and frequent attacks of the angina pectoris syndrome, which were relieved by measures directed against the seasonal allergic manifestations.

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TREATMENT AND PREVENTION OF RHUS TOXICODENDRON POISONING*

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SINCE the isolation of the toxic principle of poison ivy in 1907,[1] the sequence of events, particularly in regard to prevention and treatment of Rhus poisoning, has been rather colorful. In 1907 it was found that the toxic constituent of *Rhus toxicodendron* was of a glucoside nature and was in part precipitated by lead acetate.[1] The treatment advocated was the use of potassium permanganate, and satisfactory results were claimed on a small series of one patient.[1] The chewing of the Rhus leaf, a practice dating back many years, was reemphasized in 1916 and excellent results were claimed as a preventive measure.[2] This method was brought forward again in 1932, and the chewing of a small leaf in early spring was advocated as a preventive measure.[3] That the toxic ingredient of Rhus does not injure mucous membrane is well accepted, but particularly in the child, the chewing of the leaf not infrequently leads to a dissemination of the poisonous principle on the skin around the mouth which makes this procedure rather impracticable. The next step in oral administration was the use of the alcoholic extract.[4, 5] This was given diluted in water or in capsules with milk sugar. Favorable results were claimed,[5] but the treatment required several weeks and is considered too tedious.[6] Even as an adjunct to the injection treatment the oral method merely adds to the complexity of the procedure.[5, 6] Excellent results are reported by the combined method in one series of cases, the dose varying from 5 to 15 minims hypodermically and 15 to 30 minims by mouth, depending upon severity of case.[11] In the search for a simplified method the injection treatment came into vogue. This at first consisted of the use of the alcoholic extract.[5, 6] The dosage varied from four injections[5] to ten or twelve injections.[6] Care had to be taken to avoid overdosage due to too rapid absorption of the alcoholic extract. Also in most cases there was a good deal of pain accompanying the injection due to the effect of the alcohol on subcutaneous tissues. The painful nature of these injections led to the formulation of the almond oil extract which is not painful when injected, is nontoxic and is more potent than the alcoholic extract.[7] The almond oil extract is the method of choice today. The injection method has met with its ob-

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jectors just as has every other method, and two observers claim this method has no preventive or curative value.[8] In contrast to this, another series in different hands resulted in 59 per cent immune, 37 per cent having milder attacks, and the remaining showing no improvement.[6] In another series of 26 cases, the two observers noted 15 patients improved after first dose, five showed moderate improvement after first dose and recession after second dose, five improved after second dose, and only one required a third dose.[10] With such a diversity of opinion and methods, it can be said that we have no standard acceptable procedure of prevention or treatment. New methods are still being devised, one of the most recent being daily baths for approximately one month in which the concentration is increased from 5 to 10 drops of extract in 10 gallons of water to 150 drops of concentrated extract per 10 gallons of water.[9] Immunity was claimed in a small series of cases. It hardly need be mentioned that we still have the usual diversity of local applications which are still as tedious and unsatisfactory as ever.

With the trend of modern medicine more and more toward the preventive aspect, which is as it should be, it is of interest to note some of the observations relating to the immunologic peculiarities of *Rhus toxicodendron.* Ordinary animals are immune.[8] This has no relationship to the hair content inasmuch as removal of hair and even abrasion of skin promotes no reaction. We have observed this to be true in the guinea pig and white rat. There is no local immunity.[8] Repeated attacks shorten the stages of subsequent attacks.[8] In determining human susceptibility, the percentage of immune individuals is high if the skin is not abraded, but is almost negligible if abraded skin is used for the patch test.[8] The discharge from the lesions does not disseminate the condition.[8] In the occurrence of lesions distant from points of exposure, the blood stream must be considered as a vehicle of conveyance. Indians in the Middle West are as susceptible as the white races.[12]

In reporting the following cases, it will be noted that they have been observed over a period of five years, the ages varying from five to fifty-four years, and the results have been uniformly similar. The almond oil extract of *Rhus toxicodendron* as prepared by the Lederle Laboratories in 1 c.c. vials was employed. The site of injection was the deltoid in adults and older children and the gluteal muscles in the young children. The skin was sterilized with tincture of merthiolate, injection was made deep intramuscularly, and before withdrawing the needle a large drop of collodion was placed around the spot of injection. Upon withdrawing the needle, the collodion effectively sealed the punctured skin, preventing any egress of Rhus toxin and eliminating the possibility of any local dermatitis of the skin around this area due to contact with the toxic principle. It cannot be too strongly

emphasized that the site of injection be sealed with collodion and that the site of injection should not be rubbed or massaged in any way. In no case was a local application employed. In no case was there a generalized reaction, in most cases no local reaction; and when a local phenomenon occurred, it was nothing more than a slight soreness lasting but a few hours, never more than twenty-four hours. In no case was less than 1 c.c. of extract used. Never more than 2 injections were needed.

In all cases the initial improvement was evidenced by cessation of itching and retardation of lesions. Noticeable improvement varied from one to three days after injection. In all the cases to be cited, it is to be noted that in every instance there has been an annual exposure to poison ivy. This history of consistent exposure was definitely obtained from each patient. In every case the patient was perfectly satisfied with the results and considered the injection method the method of choice in treatment and prevention.

CASE REPORTS

CASE 1.—A. L. B., thirty-five years of age, received two injections in 1928, one in 1929, one in 1930 and one in 1931. Improvement began within twenty-four hours after injection. First attack was moderately severe, the others were mild. He was immune in 1932. In 1933, had a few lesions on the arms. Received one injection, and improved immediately. In 1931 the injection was prophylactic. No lesion developed that year.

CASE 2.—L. B., six years of age. Generalized eruption was rather severe in 1928. One injection received and improvement followed. In 1929 and 1930 there were mild attacks. One injection was received each year with immediate improvement. In 1931 a prophylactic dose was given. Immunity developed in 1931, 1932 and to date, 1933.

CASE 3.—J. B., five years of age. Mild eruption on arms and legs in 1931. Received one injection and improved immediately. Immune 1932 and to date in 1933.

CASE 4.—Miss O., twenty-two years of age. Severe eruption on both legs in 1928. She received two injections forty-eight hours apart and improved after the first, and recovered after the second. She has been immune since that time.

CASE 5.—Mrs. S., about forty years of age, had severe eruption on both legs in 1930. She received two injections three days apart. She improved after first, and recovered after second.

CASE 6.—W. S. S., fifty-four years of age. Eruption was on both legs in 1927. He received one injection and recovered immediately.

CASE 7.—C. S., aged forty-five years. Eruption on both legs occurred in 1930. He received two injections forty-eight hours apart, improved after first injection, recovered after second.

CASE 8.—D. O., six years of age, received a prophylactic dose in 1932, and was immune. A similar dose was given May 1, 1933. He remained immune to date.

CONCLUSIONS

1. The almond oil extract of *Rhus toxicodendron* can be injected safely within wide age limits if the proper technic be employed.

2. The injection method, if the correct technic is employed, is a simple and efficient form of therapeusis and prevention in cases of *Rhus toxicodendron* poisoning.

3. One injection in the spring will protect susceptible individuals for approximately one year, as shown by four of the reported cases.

4. Injection of the almond oil extract not only is satisfactory therapeutically but also offers protection for the rest of the season, and leads to milder attacks the ensuing year.

5. After several annual injections, a susceptible individual may be immune for one year without treatment. This was noted in two cases.

6. After one year of treatment some susceptible individuals may be immune longer than one season. In two cases exposed annually, immunity has been present for two years in one and five years in the other.

7. *Rhus toxicodendron* poisoning is prevalent in this country and annually is a source of severe discomfort to many individuals. More emphasis should be placed on its prevention.

8. The value of any preventive measure cannot be based on a few cases. It would be well if more members of the profession would report their experiences with the employment of this method in order that it might be more properly evaluated.

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THE COMMON WEED TANSY (TENACETUM VULGARE) AS A CAUSE OF ECZEMATOUS DERMATITIS*

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WE ARE reporting the following case of dermatitis eczematosa caused by an extremely common plant which has not, so far as we know, heretofore been recognized as a possible etiologic agent of plant dermatitis.

Once the eczematous sensitization to this plan has been proved to exist, it is obviously necessary to include patch testing with this plant in investigating cases of eczematous dermatitis of unknown origin.

Tansy *(Tanacetum vulgare)*[1] is a common perennial-rooted herb of waste places, kitchen gardens and waysides, sending up from a strong crown a clump of upright stems, one to three feet high, bearing smooth, dark green, pinnately compound leaves made up of sharply toothed leaflets, the blade of the leaf running down from the petioles (Fig. 1); yellow flowers, reaching a diameter of one-half inch, occur in terminal branches, flat-topped clusters. It is a rank-smelling herb, used in medicine as an abortifacient and at one time was used by the housewife as a flavoring for omelets, pastry and other foods. It is in flower from July to September.

In the following case, both the skin tests and the clinical history and observation fulfill the criteria required by Sulzberger and Wise[2] to prove the etiologic significance of a substance in a given case of eczematous dermatitis.

CASE REPORT

Mrs. E. L., American, white, fifty-two years old, was first seen on October 15, 1931. The patient gave a negative personal and family history for asthma, hay fever and atopic dermatitis. The eruption for which she sought relief had been present for about ten days. The skin of her forehead, the sides of her face, the postauricular and deltoid areas presented a very intense erythematous and edematous eruption, made up of pinhead to pea-sized vesicles and an occasional papule. The patient denied the use of a hair dye or any other external irritant. In spite of the patient's persistent denials, all cosmetics that she used and numerous other substances were applied as patch tests. The results were all negative. Treatment with mild topical applications was instituted and the eruption disappeared completely in about two weeks.

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The patient was seen again on April 15, 1933. She had a similar but more extensive dermatitis; the eruption covered her entire face, and both eyes were completely closed. After questioning her as to the probable causative agent, she informed us that during the time between her first appearance and the present exacerbation, she had had three or four similar attacks and that this condition always occurred following her visits to her mother, who lived in Asbury Park, N. J. She remembered definitely that as soon as she walked into her mother's garden she instantaneously began to sneeze violently, and her eyes

Fig. 1.—Tansy (*Tanacetum vulgare*). (Photograph by Hogstad.)

and the skin on her face began to itch and burn. The dermatitis invariably appeared on the following day. When she returned to the city the eruption gradually disappeared and did not recur until she next visited Asbury Park.

Patch tests with the various pollens were tried with negative results. She was then advised to have her brother gather samples of the plants that grew in her mother's garden. Patch tests were performed with the leaves of all of the twelve varieties of plants gathered. There was no reaction except to tansy *(Tanacetum vulgare)*.

The application of a portion of a leaf of this plant to the normal skin of the forearm caused such severe itching and burning that at the end of about ten hours it had to be removed. The area upon which the tansy leaf had been applied revealed a sharply defined severe erythema and vesiculation. Scratch test with tansy extract caused no immediate wheal reaction. The eruption was again treated as before with a complete disappearance in about two weeks.

It was then decided to attempt to desensitize the patient by the oral method employed by Schamberg in rhus dermatitis. A decoction of tansy was first made and then a 10 per cent tincture was compounded. The patient was advised to take one drop of this tincture in a glass of water three times a day increasing the dosage by adding one drop every second day.

On the way home from the office after having received the prepared tincture, the patient decided to taste the medicine. She opened the bottle and took a swallow. She was immediately overcome by a violent fit of sneezing, accompanied by severe burning and itching of the skin. The following morning, when she was seen again, her entire face and chest (i.e., the areas previously affected) were covered with the identical eruption observed in her previous attacks.

It must be left to future observations to decide as to the relative frequency of dermatitis eczematosa caused by tansy. The frequency of such cases in view of the perennial nature of the plant, its ubiquitous distribution and the many opportunities thus afforded for contact, must depend to a great extent upon what proportion of the population it is capable of sensitizing. This question must be the object of further study.

Of course, the nature of the specific dermatitis excitant contained in *Tanacetum vulgare* is as yet unknown. Whether it be an oil such as in rhus (McNair[3]), in ragweed (Brown, Milford and Coca[4]), in oak and sumac (H. W. Straus[5]), a lactone as in *angelica sylvestris* (Peck[6]), a simple crystalline non-nitrogenous substance as in primrose (Nestler, Simpson and Bloch[7]), or a substance different from any of these remains to be decided. It will also be necessary to ascertain whether the allergen in tansy is a new one or whether this plant contains the same active principle as some other plant or plants previously known to cause eczematous dermatitis.

However, this case proves (1) that *Tanacetum vulgare* can cause a very high degree of hypersensitivity of the epidermal or eczematous type; and (2) that contact of the plant with the skin in a person thus sensitized can produce a severe dermatitis.

There is a possibility that, in our case, the dermatitis following the ingestion of the extract may have been due to a chance external contact (touching the opened bottle, volatile substances, etc.). However,

the course and appearance of the dermatitis after ingestion as well as the analogies with numerous similar eczematous eruptions after the ingestion or injection of other eczematogenous noxae[7, 8] make it at least equally possible that the excitant was absorbed and hematogenously distributed to the hypersensitive skin areas. In this event the tansy excitant must have passed through the mucous membranes very rapidly; for the time of the development of the reaction after ingestion and after contact were practically identical—this case would then also illustrate the important and now established fact that circumscribed and fixed hypersensitive areas can react with eczematous eruptions to the hematogenous distribution of noxae. (Compare quinine dermatitis.[8, 9]

In addition to these general and theoretical considerations our case shows that the common perennial tansy weed *(Tenacetum vulgare)* should be included among the patch tests employed in the investigation of cases of eczematous dermatitis of unknown origin.

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CONTACT DERMATITIS DUE TO A COMMON PLANT*

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THE development of specific skin sensitization with resulting dermatitis from contact with a variety of plants is well known. Weber,[1] in 1930, compiled a list of 121 reported plant excitants of contact dermatoses which are found in the United States, and the number of such plant irritants reported in the literature is constantly growing.[2, 3, 4] This suggests that possibly many other plants may contain irritants capable, with adequate contact, of specifically sensitizing the skin of susceptible individuals, indicating the importance, in the study of cases of dermatitis of the contact type, of investigating carefully all plant contacts. In an occupational dermatitis recently studied, the common bleeding heart, *Dicentra spectabilis*, was demonstrated to be the specific cause of the skin lesions. No report of sensitization to this plant is found in the literature. In view of the frequent use of the *Dicentra spectabilis* as a border plant in lawns and gardens and its cultivation in greenhouses, thus offering adequate possibilities of human contact, a report of this case seems desirable.

CASE REPORT

G. J. S., a boy aged nineteen years, a greenhouse worker, was referred to the Allergy Clinic on April 12, 1932, complaining of a troublesome skin eruption involving the hands, forearms and neck, and accompanied by intense pruritus. About six weeks previously he had noticed itching of the backs of the hands followed very shortly by an erythema on which there developed a vesiculopapular eruption. This spread rapidly to the fingers and wrists, then gradually involved the forearms and later the sides of the neck. Questioning elicited that at the time the skin manifestations appeared, and for a few days previously, he had been working exclusively with bleeding hearts, as was still the case at the time he reported for treatment. He had been continuously employed in greenhouses for four years, for the last year and a half in his present position. Never previously, however, had he been assigned to work with bleeding hearts, though presumably having casual contact with this plant. The plants, at the time the skin condition developed, had not been recently sprayed. There were no new factors in this patient's home environment. The

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past history, except for the facts of his employment, was irrelevant. He had previously been free from any skin disorder. There was no history of other allergic manifestations, nor was there a family history of allergic disease.

Examination revealed the skin of the dorsum of the hands, the fingers, the wrists and forearms diffusely erythematous and hypertrophied with scaly patches, exaggerations of the skin lines and on the dorsum of the hands and wrists fissuring and areas of weeping interspersed with groups of papules and vesicles. The skin of the sides of the neck showed similar changes. General physical examination revealed no other abnormalities.

The history suggested so strongly the bleeding heart as the causal agent, that the patient was instructed to avoid assiduously any contact with these plants. This was accomplished by his transfer to other work in the greenhouse. There was almost immediate relief from itching and a very decided improvement in the appearance of the involved skin in one week's time. Within a few weeks the dermatitis had completely cleared up, and with continued avoidance of the offending plants he remained entirely free of any skin disturbance until March 26, 1933. On that date his employer, who had questioned the relationship of this boy's trouble to contact with bleeding heart, insisted on his again working with this plant, the work consisting of cutting slips and transplanting them. This he did for about two hours. A few hours subsequently he noted itching of his hands followed before the next morning by an erythema on which papules and vesicles gradually made their appearance. The eruption spread rapidly to the forearms and then appeared on the neck. When seen by me three days later, these parts presented a typical acute dermatitis. By the patient's again avoiding all contact with bleeding hearts the lesions began promptly to disappear, and in approximately ten days the skin was very nearly normal.

Contact tests by the patch method were made with the pulverized leaves of bleeding heart, primrose, chrysanthemum, begonia, geranium and asters. A reaction resulted only with the bleeding heart. Over the site of application of the latter there developed an intense erythematous vesicular reaction beginning at the end of twenty-four hours and accompanied by marked pruritus. Examination on the fourteenth day showed the skin at this site still thickened, rough and scaling, with excoriation marks extending on to the adjacent skin. Patch tests made with these leaves on three normal persons gave no reactions.

An extract was prepared from the dried leaves of the *Dicentra spectabilis,* using anhydrous ether. A second was made from the leaf residue left after complete ether extraction, Coca's solution being used as the extracting fluid. A third solution was prepared by treat-

ing with 95 per cent alcohol a portion of the greaselike residue obtained by the evaporation of the ether extract. Patch tests made with the ether extract and with the alcohol soluble fraction of the ether extract residue gave pronounced reactions in approximately twenty-four hours, while similar contact tests with the leaves after complete ether extraction and with the Coca's solution extract (presumed to contain the protein fraction) gave none. A scratch test with the latter solution and one with a solution of the ether extract residue in olive oil resulted negatively.

An attempt was made to transfer the hypersensitiveness passively to three non-sensitive individuals (who were known to accept passive transfer) by the Prausnitz-Küstner method without success. Neither the test nor the control areas showed any reaction at the end of forty-eight hours.

COMMENT

The dermatitis in this patient was demonstrated to be due to a specific cutaneous sensitization to a toxic substance present in the leaves of the *Dicentra spectabilis*, and resulted from contact of the sensitized skin in his occupation.

The specific irritating principle is completely extracted from this leaf with anhydrous ether, a lipoid solvent, and is soluble in alcohol. It gave a negative skin test by the scratch method, but by its surface application to the skin, the typical lesions were reproduced. Attempts to transfer passively the hypersensitiveness were unsuccessful.

From these studies, the specific irritant of the *Dicentra spectabilis* appears to be a nonantigenic lipoid substance, similar in nature to the other vegetable excitants of contact dermatitis so far studied.

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EXTREME HYPERSENSITIVENESS TO HEAT

Report of a Case*

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LITTLE attention was paid to the frequently observed instances of undue susceptibility to temperature changes until Duke[1] advanced his theories of the pathologic physiology involved and outlined rational diagnostic and therapeutic procedures. Tests for thermal hypersensitiveness have been used routinely in the study of patients in the Allergy Clinic of the University of Virginia Hospital for the past year. One patient was so extremely sensitive to heat and was so satisfactorily desensitized that we herewith report the case.

CASE REPORT

A forty-three-year-old white married female was admitted to the University of Virginia Hospital for treatment of a severe typical asthmatic attack of three weeks' duration. She had had mild asthmatic symptoms almost daily for three years with occasional severe attacks, usually precipitated by acute respiratory infections with fever and purulent sinusitis.

The present attack was precipitated by an acute respiratory infection with fever but no demonstrable sinus infection. An allergic history revealed that the asthma was aggravated between severe attacks, by hard boiled eggs, tomatoes, white bread, onions, milk, tobacco smoke, dust, feathers, dampness, quick changes in the weather, and heat from a stove. Scratch and intradermal skin tests were positive for wheat, milk, sea trout, egg white, tobacco, feathers, stock and house dusts and monilia. Orange, string bean, several danders, yeasts, and molds gave doubtful reactions.

Her fever, which was 100° on admission, and her acute dyspnea subsided markedly within three days after admission. On the fourth day, when she was subjectively and objectively comfortable and only a few asthmatic râles could be heard with the stethoscope, her chest was exposed to heat from an infra-red lamp. Within thirty seconds she complained of feeling smothered and began to cough. A typical asthmatic attack followed immediately. The lamp was removed and ice placed on her chest. In one minute she began to feel better, in four minutes she was completely relieved and very few râles could be heard in her lungs. The test was repeated immediately with identical results.

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The next day a hot water bag, just warm to the hand, was put on her chest. In less than one minute she began to cough. A typical asthmatic attack followed almost immediately. The hot water bag was replaced by an ice bag. In one minute she felt better. In two minutes she was completely relieved. This procedure was repeated daily for four days. Each day the attacks occurred more quickly until on the fourth day the asthma began seven seconds after the hot water bag, at 88° F., was placed on her chest. The ice bag relieved this attack in about thirty seconds.

Such extreme reaction to heat suggested testing with less heat. Accordingly an ordinary forty-watt desk lamp was shone on her chest from a distance of one foot. She began to cough and wheeze within ten seconds. She was relieved in forty seconds by the ice bag. This was repeated several times with similar results.

Although the asthmatic attacks produced by the heat were accompanied in each case by the sudden appearance of typical asthmatic dyspnea, squeaks and râles, and although these signs disappeared almost as suddenly when ice was applied, it was thought necessary to evaluate any existing psychogenic factor in the production of the attacks. With this in view her face was covered with a towel and the lamp, not lighted, was held over her chest. She began to cough and complained of a smothering sensation in eighteen seconds. When told that the light had not been turned on she explained that the heat under the towel over her nose was responsible for her symptoms. When the towel was replaced by rubber pads held over her eyes, she did not have symptoms when the unlighted lamp was held over her chest for one and one-half minutes. The lamp was then turned on inaudibly. She began to cough and wheeze within ten seconds after the lighted lamp was held at a distance of three feet from her chest. The ice bag relieved her within forty seconds. This test was repeated several times with comparable results at first. Later she would begin to cough and wheeze about seventy-five seconds after her eyes were covered but before the lamp was turned on. But when the lamp was turned on inaudibly and held over her chest she began to cough and wheeze within ten or fifteen seconds. This discrepancy would be explained theoretically by Duke by assuming that the attacks which followed simple covering of her eyes were due to the heat generated internally by the anticipation of an attack. On superficial analysis the attacks which followed simple covering of the eyes seem comparable to the conditioned reflexes of Pavlow. The fact is that this internally generated heat or conditioned reflex took longer (seventy-five seconds) to cause an attack than the externally generated heat from the lamp (fifteen seconds).

Foreign protein shocks with intravenous typhoid vaccine were selected as the best form of therapy, in preference to graduated ex-

posures to sub-reacting amounts of heat. A preliminary subcutaneous injection of 0.2 c.c. of typhoid vaccine produced no reaction. Five million bacilli intravenously the next day produced a fever of 100°, but no chills or asthma. Exposure to heat from the desk lamp for thirty seconds the next day again caused asthma which was promptly relieved by the ice bag.

Two days later twenty-five million bacilli intravenously produced chills and fever of 102.4° in about six hours. During the fever, which lasted about twenty-four hours, she had two attacks of asthma. They were promptly relieved by the ice bag. The day after the fever subsided her chest was exposed to heat from the desk lamp for three and one-half minutes at a distance of one and one-half feet without causing the slightest reaction. The lamp was then held six inches from her chest for four minutes. She remained perfectly comfortable.

Two days later a hot water bag at 100° F. on her chest for five minutes produced no discomfort. The following day a three-and-one-half-minute exposure to infra-red heat from a distance of eighteen inches produced erythema of her chest but no asthmatic symptoms.

Five months ago she was discharged, symptom free, with routine advice as to avoidance of known aggravating foods and inhalants. In addition she was told to put a hot water bag on her chest every day for ten minutes and to follow this with cold wet cloths if asthmatic symptoms occurred. She has returned to the clinic almost every week for autogenous vaccine and house dust injections. She remained quite comfortable for three months except for one fairly severe attack which occurred at the peak of another acute respiratory infection with high fever. The paroxysms in this attack were promptly relieved by an ice bag. She has gained weight, sleeps well, has no indigestion, is doing all her housework including cooking, washing and ironing. With the onset of summer weather she began to have moderately severe attacks regularly in the middle of the day, especially while preparing the noon meal. She was given two more febrile reactions with typhoid vaccine intravenously and now has no symptoms of asthma except occasionally while sweeping or breathing smoke from burning grease or cooking the noon meal on hot days. A cold towel on her chest promptly relieves these mild transient attacks.

DISCUSSION

It is common knowledge that a large percentage of allergic patients are consciously affected by changes in temperature and humidity. Extreme hypersensitiveness to thermal influences can be demonstrated very easily by immersing the hands or feet in cold or hot water, or by applying a hot water bag or ice bag or breeze from an electric fan to the chest. Lesser degrees of thermal hypersensitiveness can be demonstrated by the nitrogen lamp, infra-red heat, diathermy or ice

baths. The various effects of humidity and contrasting temperatures can be tested in a hot or cold closed shower, or by hot or cold moist gauze over the nose while heat or cold is applied to the chest.

Detailed directions for these tests are given in Duke's[1] excellent papers. It is our wish to emphasize that thermal hypersensitiveness is an important aspect of the allergic manifestations, that it can be tested for easily, and that it is amenable to specific thermal therapy. In this case an ice bag on the chest relieved the attacks more promptly and more completely than adrenalin, and foreign protein shocks promptly desensitized her to heat.

SUMMARY

A case of extreme hypersensitiveness to heat is described. The outstanding features were: (1) Exposure of the chest to heat from an ordinary forty-watt desk lamp at a distance of one and one-half feet for thirty seconds invariably produced an attack of asthma. (2) An ice bag invariably relieved attacks in three or four minutes or less. (3) The patient was promptly desensitized to heat by foreign protein shocks from typhoid vaccine intravenously.

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URINARY PROTEOSE IN ALLERGIC CONDITIONS*

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IN 1928 Oriel and Barber[1] reported the presence in the urine of allergic individuals of a specific, ether-extractable substance, to which was later given the name of "urinary proteose." This substance was found to increase in amount in the active stages of the allergic or anaphylactic state, coincident with other biochemical findings in the urine taken to indicate a functional disturbance of the liver. Subsequent reports[2, 3, 4] stated that while this substance was found present in small amounts in normal individuals, it was present in larger amounts in nonallergic conditions such as tuberculosis, influenza and pneumonia, and in such allergic conditions as asthma, eczema, urticaria and migraine; finally recovery from the active stages of these allergic conditions was marked by a decrease in the amount of this proteose. In the allergic patients positive skin reactions could be obtained with the specific proteose, these reactions decreasing in intensity as the condition subsided. Chemically this substance seemed to be in the nature of a proteose, and immunologically it was found capable of acting as an antigen: thus, with the use of human serum, Oriel reported the ability of passively sensitizing a guinea pig uterus by the Dale technic, also the human skin by the Prausnitz-Küstner technic; and furthermore that desensitization of the sensitized guinea pig uterus could be accomplished. In conclusion, these authors stated that they believe this proteose is produced by the sensitized cells of the liver, that it is responsible for the actual symptoms of the disease and is excreted in the urine as an antigenic moiety. Therapeutically, they obtained the following results from the use of the specific proteoses in various skin conditions: Of 19 cases of chronic urticaria and angioneurotic edema, 16 were entirely free of attacks; of 13 prurigo cases, 9 patients were practically cured of all itching. In Besnier's prurigo ichthyosis cases, the prurigo was materially lessened and asthma greatly relieved.

Since the appearance of these publications, confirmatory results were reported by Darley and Whitehead[5, 6] in March, 1931. From studies in 34 cases, they reported that although they could find no quantitative relationship between the quantity of proteose obtained from the urine and the degree of skin reaction, yet therapeutically, they obtained encouraging results in asthma, hay fever, urticaria and

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subdeltoid bursitis, improvement, for example, resulting in 6 of 9 cases of asthma (the length of time this persisted, however, is not stated).

In January, 1932, Murray Lyon, Percival and Stewart[7] reported a similar study. By using a 1:10,000 dilution, 6 of 8 patients with serum urticaria gave positive results to their own and other proteoses. In 2 cases skin reactions were negative to all proteoses. Nonspecific reactions were obtained in normal individuals; also, some allergic patients gave reactions to proteoses of other patients. These authors therefore seriously doubted the specificity of the proteose they obtained and also that of the specific proteose sent them by Oriel.

Our interest in this subject began in 1931, during the course of some biochemical investigations in serum sickness carried out by one of us (L. T.) in conjunction with H. L. Brown of the Research Institute of Cutaneous Medicine, Philadelphia. At this time, studies of the urine for "proteose" were carried out upon 2 patients who had received serum in large amounts, the urines being collected both before and at frequent intervals after the injection. While definite amounts of proteose were obtained, in neither instance could positive skin reactions be obtained with various dilutions of the proteose.

In an effort to learn more about this reaction, it was decided to make a more complete study in patients suffering from various allergic conditions in order to determine definitely whether the claims of Barber and Oriel could or could not be substantiated.

MATERIAL

Three groups of patients were studied—one as a control group consisted of nonallergic normal individuals recruited from the student or nursing staff; the second, of ward patients suffering from various types of nonallergic conditions, and the third group consisted of patients presenting various types of allergic conditions including asthma, hay fever, two cases of urticaria, and one of migraine. In the allergic group an attempt was made to collect one specimen during a paroxysm and a second specimen during a quiescent period in order to detect any variation. In the patients with hay fever, specimens were obtained before the season, during the season when symptoms presented themselves, and after the season had finished. In all these instances quantitative estimations of proteose were made, and also skin tests.

TECHNIC

In carrying out this technic we took particular care to follow as specifically as possible the directions given by Oriel: A twenty-four-hour specimen of urine was collected, using chloroform as a preservative. Four hundred c.c. of this were made acid to Congo red with 25

per cent sulphuric acid. If urates were present they were dissolved in dilute sodium hydroxide and the urine was acidified. One hundred c.c. ether were then added and the mixture was shaken. The ethereal layer was separated, then treated with an equal amount of alcohol (100 c.c.) and the precipitate allowed to settle. It was then centrifuged in a sterile graduated centrifuge tube, which was placed in the incubator until the ether and alcohol evaporated. For quantitative purposes, the amount present in the tube was read and the percentage estimated per 100 c.c. For the skin tests, the precipitate was dissolved in 2 to 3 c.c. sterile N/10 NaOH. One c.c. added to 9 c.c. of 0.5 per cent phenol in normal saline was considered a 1:100 dilution, and from this were made up 1:1000, 1:10,000, 1:100,000 and 1:1,000,000 dilutions, which were then used both in skin testing and for therapeutic purposes. Skin tests were performed by the intradermal injection of 0.025 c.c. of each of the five dilutions, using the proteose obtained from a normal allergic individual as a control. Reactions were read in ten minutes and classified as ± (doubtful), slight, moderate or marked according to Cooke's classification.

RESULTS

These are shown in Table I. As can be seen from the figures obtained, the amounts of proteose varied greatly in all the groups, the

TABLE I

GROUP	NO. PATIENTS	NO. URINE EXAMINATIONS	PROTEOSE IN PER CENT LOWEST	HIGHEST	AVERAGE
Nonallergic Normals	16	16	0.12	0.35	0.18
Nonallergic Medical Conditions Excluding Cardiovascular Renal	27	27	0.08	0.50	0.22
Allergic Asthma Including 2 Urticaria and 1 Migraine	18	25	0.07	0.80	0.29
Hay Fever	24	36	0.05	1.4	0.33
Cardiovascular Renal	18	18	0.15	2.60	0.64

greatest variation and largest amounts occurring in the cardiovascular group, no doubt as a result of the increased renal permeability in these conditions. In the allergic group somewhat larger amounts were noted than in the nonallergic controls, and of the two allergic groups a higher average was obtained in the hay fever than in the asthma group. In the hay fever group, 22 specimens were obtained during the active stage and 14 during the inactive, but on averaging the amounts of proteose in these two subgroups, they were found to be equal (0.33 per cent). In 11 of these patients specimens were obtained

in the active and also in quiescent periods. In 7 there was an increase of proteose during the active stage, in 3 a decrease and in 1 there was no change. In 5 of the asthmatic patients additional specimens were obtained at other times when the patients again presented symptoms. All these specimens showed a variation in amount ranging between 0.05 per cent and 0.24 per cent.

Skin tests were done only in the allergic group. Of the asthma group, 12 were skin tested. In 8 of these completely negative reactions were obtained in all the dilutions and also in the control. In 4 patients slight reactions were obtained with the 1:100 dilution, but in these a similar reaction was obtained with the same dilution of the control or with normal proteose. Of the hay fever group, 30 tests were made. Of these 19 showed completely negative reactions in all dilutions and in the control. In 4, slight reactions were obtained in the 1:100 dilution but showed similar reactions in the control. In the remaining 7, slightly larger reactions were obtained in the 1:100 dilution of the autogenous proteose than of the control, but because of the apparent toxicity of the 1:100 dilution there was never sufficient difference to be considered specific. In no instance could positive skin reactions be obtained with any of the higher dilutions such as 1:100,000 or 1:1,000,000 as reported by Oriel.

Because of our failure to obtain specific skin reactions in the allergic group, skin tests were not considered necessary in the nonallergic groups.

Treatment with the autogenous proteose was carried out in 3 cases of long-standing asthma rebellious to all other forms of treatment. No improvement was noted in any of these cases. These findings are similar to those reported recently by Trasoff and Meranze[8] in a group of eight asthmatics.

DISCUSSION

From the foregoing experiments it is obvious that by the use of ether it is possible to extract from the urine a substance possibly in the nature of a proteose, obtainable in small amounts in nonallergic individuals either during health or with various types of illnesses exclusive of cardiovascular renal disease, in larger amounts in such allergic conditions as asthma or hay fever, and in largest amount in individuals with cardiovascular renal conditions of various types. While it appears that during the stage of active symptoms in the hay fever patient an increased amount is excreted, this is not particularly evident in the asthmatic patients, in whom the amount varies from time to time. Qualitatively a specificity of the proteose is not demonstrable, since its presence is not limited purely to allergic conditions.

From an immunologic standpoint, results of the skin tests fail to demonstrate any specificity of reaction, since positive reactions were obtained only with a dilution which because of its toxicity gives rise in many patients to a nonspecific reaction. In the higher dilutions completely negative reactions occurred.

It is difficult to account for the variations in results of skin tests obtained by Oriel and his coworkers and by others. It must be borne in mind that skin reactions and their interpretation are variables that depend considerably upon the character of the patient's skin, the amount of material injected and the experience of the observer. Those familiar with the intradermal method of testing know very well that certain reactions which may be considered positive in an individual with a nonreactive or insensitive skin might be considered negative in an individual with a very reactive or sensitive type of skin. Furthermore, the use of 0.025 c.c. as recommended by Oriel is more than is ordinarily used in the intradermal method of testing (about 0.01 c.c. is the average) and may be productive of nonspecific reactions, unless adequate controls are used coincidentally.

In view of these considerations and of the results obtained, we must agree with Freeman[9] in his conclusions from a study of the specificity of proteose intradermal reactions in a large series of hay fever and asthma patients, that (1) "Oriel's proteoses no matter whence obtained or on whom tested show a fairly constant toxic reaction within a few minutes of injection into the skin; (2) no trace of the specific skin reactions claimed by Oriel could be found; and, finally, (3) an immunotherapy based on this alleged specificity has no scientific foundation."

CONCLUSIONS

Although the presence of an ether-extractable substance described as "urinary proteose" by Oriel, could be demonstrated in the 61 examinations of the urine of 42 allergic patients in slightly larger amounts than in the nonallergic controls, and although larger amounts were eliminated than in the quiescent periods, yet positive skin reactions of a specific character could not be elicited nor was treatment in three cases of chronic asthma followed by any improvement. It is doubtful from these observations and review of the literature whether the proteose of Oriel has a specific immunologic basis.

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THE TREATMENT OF BRONCHIAL ASTHMA BY STERILE ABSCESS FORMATION

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ANY procedure which will benefit refractory cases of bronchial asthma certainly needs no apology for its introduction. Any one who treats bronchial asthma knows that, whereas the results obtained in a great majority of cases are highly satisfactory, there are cases in which no results, or at the most, very slight benefit can be obtained no matter how hard one tries and irrespective of the course pursued.

Where it is impossible to establish the etiologic factor of asthma, the results of the treatment are particularly poor. Not infrequently the cause of the trouble is apparently clear and established, either from the history of the patient or from the positive skin tests; yet no results can be obtained even when one eliminates the allergen, or desensitizes the patient where exclusion of the allergen is impossible. The elimination of focal infection; the injection of pollens, vaccines (both stock and autogenous), tuberculin, foreign proteins, and all sorts of chemicals; autohemotherapy; the administration of endocrine substances, drugs, and electrotherapeutics will sometimes fail even in cases wherein, as a result of previous experience and logical reasoning, one has a right to expect good results. In these cases of asthma, the shock treatment, produced by intravenous injection of vaccine, such as typhoid, will often yield good results. The dose of the intravenous vaccine may be made so small that no symptom of shock is produced, but only a temperature of 101° to 102° F., headache, discomfort, or even no symptoms whatsoever, and yet good results will be frequently obtained by a series of about 12 of such injections given twice weekly. However there are, though fortunately rare, cases in which all the above mentioned procedures fail. It is in these cases that I establish a sterile abscess and obtain good results in the great majority of cases.

I presented, in 1919, before the Brooklyn Society of Internal Medicine, a dozen such cases of bronchial asthma treated by the formation of sterile abscess, with uniformly good results. Since then I have had 25 more cases. Some of them, however, failed to respond even to this treatment.

The reason for my first employing the sterile abscess formation in the treatment of refractory cases of bronchial asthma is the history given by one of the patients. His sister had had asthma for

years, until after her confinement when she developed a "big abscess on her side," and since then, for the last twenty years she has been free from asthma. I also had the histories of 2 patients who had had asthma for years and who had received many and various hypodermic injections. Each developed an abscess following an injection. Both patients were free from asthma for a period of over a year thereafter. I determined to reproduce this phenomenon as closely as possible by the formation of a sterile abscess.

I inject subcutaneously in the arm, or any other place, 1 to 2 c.c. of spirits of turpentine. A swelling appears in from four to twenty-four hours after the injection, and on the second day there are all the signs and symptoms of abscess formation. As soon as the abscess appears, the asthma disappears, as a rule. In some cases large quantities of secretions are coughed up for about three days. Thereafter, this gradually disappears completely. The patients so treated sleep well and all signs and symptoms of asthma disappear either abruptly or gradually. Very often the change for the better is like the crisis of pneumonia. The temperature varies between 101° and 105° F. There are a leucocytosis and polymorphonucleosis in every case, sometimes as high as 44,000 leucocytes and 93 per cent polymorphonuclears. No abnormal ingredients appear in the urine. The pain caused by the sterile abscess varied greatly, usually a moderate amount in every case. Some patients complained of no pain and a small number complained bitterly of the pain. The pain lasted until the tension of the abscess was relieved, which occurred when the pus was evacuated by an incision or by a spontaneous discharge. This occurred at the end of about a week. After the pus was discharged, the sterile abscess healed invariably without any trouble. A wet antiseptic dressing was applied to the wound until healing was complete. As a rule one sterile abscess was sufficient to get good results; sometimes a second and third abscess had to be made before good results were obtained.

The results obtained seemed to be temporary in some cases and permanent in others. This is illustrated by the following four different types of cases.

CASE 1.—L. W., male, fifty-five years of age, had typical attacks of bronchial asthma and hay fever for twenty-five years. These frequent and severe attacks came particularly in June, July, August, and September, when they were practically continuous. He suffered from severe headaches and skin eruptions of various kinds. He had an asthmatic sister who had developed an abscess after a confinement and who had been free from asthma ever since—a period of over twenty-five years. Fifteen years previously he had had a nose operation, without improvement. On physical examination, he presented typical asthmatic breathing. All laboratory investigations were negative. Numerous skin tests performed with various pollens, animal emanations, foods, dust, etc., were negative. He received all sorts of treatments with drugs, vaccines, pollens, etc., with no results. In September of 1919 I made a sterile abscess by injecting 1.5 c.c. of spirits of turpentine. This abscess

took its usual course. His asthma stopped twenty-four hours after the injection. With the exception of very slight and very infrequent attacks during June, July, August, and September, which were readily relieved by calcium iodide, he was perfectly free from asthma for thirteen years. In June, 1932, he again suffered from severe bronchial asthma, which, however, yielded to the usual treatment of calcium iodide.

Comment: A very refractory case of bronchial asthma of twenty-five years' duration that defied all treatments, was greatly benefited for thirteen years by the formation of sterile abscess.

CASE 2.—B. B., male, aged twelve years, weight 83 pounds, had suffered from severe attacks of bronchial asthma, hay fever, and various bizarre rashes, such as eczema, acne, hives, angioneurotic edema, etc., since birth. X-ray examination of the lungs revealed a marked peribronchial and hilum infiltration on both sides, and an x-ray diagnosis of chronic bronchitis was made. Skin tests showed that he was sensitive to various foods, pollens, and animal emanations, particularly wool. After the exclusion of specific allergens, he was entirely free from all symptoms. Unfortunately this state lasted only a short time. One by one allergic manifestations returned. Autogenous vaccines, autohemotherapy, the various drugs used in allergy, tonsillectomy, pollen immunization, wool immunization, each in turn had a temporary beneficial effect. A sterile abscess was produced in June, 1922, and it was not evacuated for over two weeks. The patient greatly improved, gained markedly in weight, and has remained free from all allergic symptoms, including bronchial asthma, for the past eleven years.

Comment: Temporary benefits only were derived from various therapeutic procedures. Lasting benefit was derived only after sterile abscess formation.

CASE 3.—D. W., female, aged nineteen years, had been suffering from severe forms of bronchial asthma for seven years. This was always worse during the winter months. Tonsillectomy, nose operations, various medications, and vaccine injections gave no results. In 1916 I injected 1.5 c.c. of spirits of turpentine and made a sterile abscess which was not evacuated for two weeks. Her asthma disappeared from that day on to the present date. In 1927 the patient developed hyperthyroidism.

Comment: A severe case of perennial bronchial asthma, worse in winter, remained free from all symptoms for seventeen years, after the sterile abscess formation.

CASE 4.—A male, aged sixty-seven years, a brewery worker, gave a history of cough and typical asthmatic attacks for years. The attacks grew worse in the last three years and for two weeks before admission to the hospital, April, 1933, they persisted continuously. Physical examination revealed all signs and symptoms of typical bronchial asthma and emphysema. The nose was clogged with mucopurulent discharge. The heart sounds were of poor quality. X-rays of the sinuses showed cloudiness in both antra. Those of the chest showed marked mottling in the lower part of both lung fields suggestive of bronchitis with bronchiectasis. The sputum was mucopurulent, with many pus cells and moderate staphylococcus, streptococcus, and pneumococcus content. All the orthodox methods employed to relieve asthma as well as the efforts of the nose specialists having failed, a sterile abscess was formed by injection of 1.5 c.c. of spirits of turpentine in the arm on May 5, 1933. Within twenty-four hours the asthmatic attack became less and less severe until at the end of forty-eight hours the patient was absolutely free from all signs and symptoms of asthma. Fluoroscopy and x-ray examination of the chest on June 2, 1933, revealed no change from the one taken prior to the abscess formation.

Comment: X-ray examination twenty-eight days after the abscess formation revealed no changes from the one taken prior to the injection of turpentine, although the patient was free from all signs and symptoms of asthma.

It is difficult to say exactly how a sterile abscess benefits these patients. Any one with extensive experience in bronchial asthma and other forms of allergy has undoubtedly seen patients in whom acute infectious disease, such as erysipelas, scarlet fever, etc., has had a marked therapeutic effect. Sometimes the reverse is observed, particularly after pneumonia and bronchiectasis, when asthma is aggravated.

A sterile abscess formation may benefit bronchial asthma in several ways: (a) by acting as a foreign protein, (b) by producing a continuous high temperature, (c) by stimulation of the immunomechanism of the body in a way unknown to us, (d) by exerting a profound influence on the vegetative nervous system.

By analogy one would expect good results with this method of treatment in other forms of allergy as well as with bronchial asthma. I have had no experience with such cases. The good results obtained in refractory cases of asthma have been so striking that I deem it justifiable to make this report, in order that others might employ this harmless procedure so that we may learn as soon as possible its indications, limitations, and, in general, its true scope.

SUMMARY

In some cases of asthma it is impossible to determine the etiology and in others in which the etiology is apparently established, all efforts toward treatment are barren of results. In such cases sterile abscess formation has yielded good results. This treatment is apparently harmless.

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36 PLAZA STREET.

Society Proceedings

THE SOCIETY FOR THE STUDY OF ASTHMA AND ALLIED CONDITIONS (CONTINUED)

NINTH ANNUAL MEETING, WASHINGTON, D. C., MAY 6, 1933

Some Observations on the Etiology and Nature of Chronic Hyperplastic Sinusitis. R. C. GROVE AND R. C. COOKE, New York City.* (Abstract.)

There is no accepted consensus of opinion as to the etiology of chronic hyperplastic sinusitis. Present theories are (1) the allergic (noninfective), (2) bacterial (infective), (3) allergic plus secondary infection. We believe the hyperplasia is due to a primary bacterial infection in a sensitized membrane. A group of 80 hyperplasias was studied from the clinical, bacteriologic and pathologic standpoints. We believe the membranes are primarily infective because (1) frequency of recovery of organisms from membranes, 43.4 per cent showing a different organism from those recovered in any previous surface cultures, (2) true skin-sensitive cases without infections rarely show hyperplastic changes, (3) with autogenous vaccines local tissue sensitization can be shown. We believe the infective hyperplastic membranes are allergic because (1) positive allergic antecedent history is frequent, (2) presence of other allergies in 30 per cent of cases, (3) frequency of skin sensitizations, (4) eosinophilia in sinus washings and membranes, sputa and blood, (5) sensitization of sinus membranes as demonstrated with autogenous vaccines and lipiodol injections.

DISCUSSION

DR. RICHARD A. KERN, Philadelphia, Pa.—I was very much interested in this presentation because by somewhat different routes we have come to rather similar conclusions. If one studies a large series of individuals with chronic sinus disease, not merely sinus disease as occurring in the suspected allergic individual, the asthmatic or the vasomotor rhinitis patient, but also in large groups of nonallergic patients, for example, bronchiectasis with their practically 100 per cent sinus infection, in other conditions of the lower respiratory tract attendant with large amounts of purulent sputum, such as chronic lung abscess, tuberculosis

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with ulceration and mixed infection, and compares that series with what one finds in the allergic group, one is struck in the first place by the difference in the appearance locally. In the nonallergic patients with simple sinus infection one finds primarily a red, a congested mucosa, not this pale, hypoplastic, swollen mucosa we have just heard described, and what is particularly striking, no polypoid degeneration, even in the presence of the most advanced and marked infection. As a result of our observations, we are willing to conclude that the presence of polyps in the nose is in itself a pretty certain evidence of allergy. As to whether that allergy is bacterial allergy primarily or not, we are not quite as willing to go as far as the reader of the paper, although the evidence is suggestive.

If we examine pollen cases during the pollen season, there is plenty of evidence of apparent abnormality in the antra on transillumination and x-ray. Yet if we examine these patients just before or only a short time after the season, we find no more sinus involvement than in a group of normal controls. In fact, in our experience, the x-ray evidence shows their sinuses to be in better condition than the average population in our city. However, just as soon as the allergic state is perennial, that is, a vasomotor rhinitis or asthma, and it matters not which, the incidence of the sinus involvement is extremely high: 89 per cent, for example, in our vasomotor rhinitis cases, and 87.5 per cent in 400 asthmatics. In the hay fever group we have purely the swelling of the antrum mucosa, just as the nasal mucosa swells in response to the pollen excitant. There is lacking, however, in that season of the year the infective agent. In those nasal conditions of hypersensitiveness which occur at other times of the year, however, the element of infection promptly steps in.

As perhaps some evidence of bacterial allergy in these cases, one might cite those patients who develop unusual reactions when given even very tiny doses of vaccines—and it is in these patients particularly that one should be extremely cautious in scheduling the dosage. I have seen a patient thrown into a violent attack of asthma when given a dose of 1,000,000 streptococci. The patient continued to get marked general reactions as well as local nasal congestion until the dose was lowered to 20,000 organisms.

Dr. Harry Lee Huber, Chicago, Ill.—I would like to ask if there was any attention paid to the sex. Dr. Rackemann has pointed out that in this group of patients, 70 per cent of them were females. I have been especially interested in a study of this group and have found just about the percentage Dr. Rackemann has pointed out. Recently the author of an article that appeared in one of our medical journals, pointed out the relationship of rhinitis to gynecological disease.

If we will look over the literature and examine these cases carefully we may find some very definite reason for this association. I think all of you have seen patients who have a severe rhinitis at the beginning of a pregnancy. It is also a very common symptom at the menopause.

Allergists should keep this suggested relationship in mind when they are studying the so-called nonallergic vasomotor rhinitis.

DR. R. C. GROVE.—In regard to Dr. Kern's discussion of the allergic reaction of the sinus membranes during acute hay fever, I think we see that, but we do not see it as frequently as most other men seem to see it. In the ones that caused any trouble, we have shown by x-ray after the season passed, that they had a hyperplastic membrane there. Of course, we all know that after an acute suppuration, the sinus membrane may go back to normal.

As to Dr. Huber's discussion about the sex, I do not have exact figures but I think our cases were about equally divided.

Status Asthmaticus or Severe Subacute Asthma. J. A. CLARKE, JR., Philadelphia, Pa. (For original article, see page 481.)

DISCUSSION

DR. FRANCIS M. RACKEMANN, Boston, Mass.—I think this paper is very timely and I believe there is a broad aspect to it. I believe that one difficulty I have, and I dare say that the rest of you have in dealing with your contemporaries at home is that they get the impression from our publications and our talks that all this allergy is rather superficial and rather easy and that the results are very good. They think that all our patients do well and that they all recover eventually or at least that they do not get much worse. Of course, by and large that is true, but it has certainly been striking lately to see the considerable number of patients like those whom Dr. Clarke has described, in whom the condition is very serious. A certain number of them have died. At the Massachusetts General Hospital Dr. Tracy B. Mallory is in the process now of studying the postmortem findings. The results will be published soon.

I should like to comment on one or two points. First of all, treatment is extremely difficult, as Dr. Clarke has said. In Boston, we have put "chronic severe" cases in dust-free rooms. We have had them in an oxygen tent for considerable periods of time. We have tried Rowe's diet. We have done skin tests but these things have been of little practical help. The intracutaneous tests are almost always negative. We have tried in every way to eliminate foreign substances, both in dusts and foods. Ordinary allergy would seem to be excluded.

The second point concerns the physical findings; that almost all of these patients have varying degrees of nasal sinusitis and it is inter-

esting that they almost all have an eosinophilia which may run up to over 20 per cent. The physical signs in the chest vary on the two sides and you will hear areas of coarse râles in one place or the other. Sometimes the breathing is unusually loud, almost "roaring." If you will listen to the same chest after a time, perhaps within three or four hours, you will find that the coarse râles have changed and that the "roaring" has changed to another area. At the postmortem, the reason for these signs becomes clear. The bronchi seem to be truly plugged with a very tenacious mucus, the degree of which varies in certain localities. The change in physical signs is due to the change in location of those bronchial plugs. The condition is serious, and the prognosis should always be guarded.

Dr. George L. Waldbott, Detroit, Mich.—The condition which Dr. Clarke describes has, I believe, a definite bearing upon observations which I have made and intended to present at this meeting on a condition which has been termed "thymic death." I have studied a series of 102 cases of which 68 were eliminated because of the presence of other conditions which somewhat complicated the picture. In 7 of the remaining 34 cases a syndrome occurred which is probably the type of "asthma" to which Dr. Clarke refers, manifested by dyspnea, wheezing, stridor, râles, shock and fever. It seems to occur very rarely. Pathologically, as well as clinically, it is distinct from severe asthma. I am inclined to call this syndrome protracted anaphylactic shock for reasons which I have outlined in my paper. The occurrence of fever which usually is present on the second or third day following the onset probably indicates a tendency to organization of edematous areas in the lungs.

In some of these cases a large thymus is present; in others there is no evidence of an enlargement of the thymus, but usually the lymphoid tissue throughout the system is hypertrophied. The characteristic findings in all these cases is capillary dilatation in the lungs and extravasation of blood cells and edema fluid into the tissue. In addition there are areas of emphysema and atelectasis. Hypoplasia of the adrenals is usually found. I have sections of cases where no adrenal medulla was present. Of course it is extremely difficult to demonstrate in the individual case the antigen which accounts for death. Nevertheless I feel that this subject deserves a great deal of consideration before a group of men such as this.

Dr. J. Harkavy, New York City.—Death in asthma, in status asthmaticus is a very horrible sort of thing to witness. What is more important, it is very difficult to treat, as has been indicated by Drs. Rackemann and Clarke. I should like to add to what has been said that in my experience, when you are dealing with a case that you think is an

allergic asthma, you have to be exceedingly careful in giving morphine, especially where adrenalin does not do any good and you have to do something. I think I have been responsible for one death as a result of giving morphine and I have seen other doctors apparently justified by the exigency of the occasion have had similar accidents. We must always remember that an allergic person can be or become sensitive to morphine, particularly inasmuch as he has in all probability already received morphine from others.

And yet in dealing with a severe status asthmaticus case, the keynote in the treatment is sedation. How are you going to get it? I have recently had a patient who presented such a problem. What we did was to give that patent an ampule of seven grains of sodium amytal intravenously in order to get her under and followed it up with sodium amytal intramuscularly until she was completely unconscious. She slept for three days. That was the only way in which we could get control of the paroxysm. Of course, you have to bear in mind the fact, that sodium amytal is a barbituric derivative and you have to look out for sensitivity to this group of drugs. But the one thing to do which is most important in order to save your patient is to get him quiet.

Another important feature to combat is the marked cyanosis in some of these patients. I have been frequently in a quandary as to whether it is due entirely to the mucus that is occluding the bronchus and inducing atelectasis and anoxemia or whether they have in addition actually an arterial spasm of the pulmonary vessels similar to that of a rabbit, and thus precipitating right heart failure. These individuals also breathe very shallowly and very rapidly, they wash out a lot of carbon dioxide in doing so. They therefore get up a secondary anoxemia because of the so-called Bohr effect. As you know this is brought about by washing out the CO_2. As a result, the oxygen is held very much more tightly by the hemoglobin and thus the tissues become anoxic, because you need carbon dioxide in order to dissociate the oxyhemoglobin. It is important therefore that these patients should be given oxygen and CO_2 and be put in oxygen tents to combat this state.

Another thing which I have also found of help is venesection. Whether it acts by reflex mechanism or in some other way, I do not know, but the patient seems to breathe much more deeply and much more quietly. You do not need much for your venesection; about 100 c.c. of blood will be sufficient. These therapeutic measures may fail completely, when we come up against it.

DR. HYMAN.—I would like to ask Dr. Clarke whether there has been fever in any of these cases.

DR. A. H. W. CAULFEILD, Toronto, Canada.—The picture that we have been given as a clinical picture as discussed by Dr. Clarke, Dr. Racke-

mann and others, has been varied, and everybody has stressed that treatment is extremely difficult. I would like to emphasize what the last speaker has said and suggest that apart from allergy, although they are allergic to begin with, a very large factor in a number of cases is atelectasis. I make that suggestion for the reason that I was able in one year to collect, I think it was 13 cases of atelectasis without any preceding operation. Usually we think of massive collapse or atelectasis as purely and solely following surgical operation. I am convinced it appears much more frequently and might be an explanation in some of these cases of the unusual clinical course and physical signs. The only way to prove atelectasis is to get an x-ray at the particular time. I was surprised to see when we did that on those cases how frequently we could prove an atelectasis. Even the radiologist came over from his point of view that it was bronchopneumonia for the simple reason the mediastinal contents were drawn to the side on which the shadow appeared.

Dr. Louis Tuft, Philadelphia, Pa.—I would like to ask Dr. Clarke how frequently these paroxysms were repeated in these patients, and if so, of what duration they were? I ask this because of a patient who has now been in the Temple University Hospital for six months, a patient of fifteen years of age who has had at least five or six such paroxysms of what might be called a bronchopneumonia with a temperature of 103, a pulse rate at times of 160 to 180, with the cyanosis that Dr. Harkavy alluded to; a patient who becomes extremely toxic and who looks as though death were imminent in these paroxysms.

On each occasion, after heroic therapeutic measures, the temperature and the pulse came down and there was a freedom from the attack. After the third paroxysm, by x-ray we found a partial atelectasis in the right lower lobe which we took to be an effect rather than a cause.

I wondered in these patients whether there was an obstructive phenomenon as a result of accumulated secretions because each paroxysm seems to be initiated by the cessation of cough. When the patient could not cough up the expectoration, this was the signal for an oncoming attack in each instance.

We have given this particular patient as much as 25 to 30 minims of adrenalin every hour without any effect and finally resorted to adrenalin intravenously, a half c.c. of a 1-1000 dilution which brought about the only beneficial effect we could produce with the exception of the use of glucose intravenously.

Dr. Horace S. Baldwin, New York City.—I am particularly interested in the patient with a chronic asthmatic state who develops an acute influenzal or other infectious bronchitis and as a result is crit-

ically and dangerously ill. Here, I believe, is where oxygen therapy exerts its greatest help in the treatment of the asthmatic. In my experience the best tents available at the present time are the large and comfortable ones such as those modeled by Barach and Thurston or Barach and Davidson. With these the patient is usually cooperative, they are easy to operate, and allow for an oxygen concentration of 50 per cent. Unless a suitable tent can be obtained I believe the double nasal catheter with the oxygen running as fast as possible offers the greatest help.

Just as in pneumonia the too lavish use of morphine is fraught with danger especially in the matter of respiratory embarrassment; the same holds true with the asthmatic confronted with a superadded infectious bronchitis or pneumonia. Only here the possibilities of danger are even greater. If the dosage of morphine is never allowed to exceed one-eighth or sixth of a grain most of the trouble will be avoided.

Finally, one of the most important measures in the treatment of chronic status asthmaticus, I am sure, is to have the patient away from his home preferably with a reassuring and capable nurse in a hospital, and institute a régime of the Weir Mitchell type.

Dr. Milton B. Cohen, Cleveland.—There is just one thing we found useful in addition to the things suggested and that is the procedure that the surgeons have adopted for handling some of their very ill patients, namely, continuous venoclysis. Occasionally these individuals in status asthmaticus need adrenalin intravenously as suggested by Dr. Leopold. If you put a cannula in a vein and hook up one of these affairs, you can give glucose and salt solution and any other supportive things you please at a regular rate and you can hook up a tube and let your epinephrine solution run in at a constant rate. So if you find you get a relief from a certain amount of epinephrine, you can maintain it over a fair period of time, instead of having the ups and downs of intermittent dosage.

Dr. C. G. Weston, Glen Ridge, N. J.—One question I should like to ask Dr. Clarke. Have you used the combination of oxygen and carbon dioxide in the treatment of severe attacks? I wish also to stress the value of glucose infusions as a supportive measure.

Dr. Harry Lee Huber, Chicago.—In at least three published reports on pathology of asthma it was pointed out there are areas of atelectasis. I think we do not need to question that there is atelectasis. I would like to ask Dr. Clarke if he has tried the ether enema and chloral hydrate enema. There have been some papers reported on the favorable use of these.

Dr. Abraham Trasoff, Philadelphia.—I wish to add one thing that was not suggested here today. This is not my own, but that of Dr.

Storm Van Leewen. A patient of mine, a young girl of nineteen, who has been asthmatic for a number of years, spent a few months in his Sanitorium in Holland. She was subject to frequent attacks of asthma and often failed to be relieved by adrenalin chloride. He suggested theocin and theobromine, 150 mg. each, and caffeine 100 mg., which gave her immediate relief. I have tried it since in numerous cases with good results. About a week ago one of my patients who was in status asthmaticus failed to be relieved by numerous drugs, including adrenalin, and I introduced 1 ampule containing 3 grains of euphyllin intravenously, with remarkable results. I mention that because it is a very useful and harmless drug and should be tried in such severe cases as described by Dr. Clarke.

Dr. W. T. Vaughan, Richmond.—There is another drug in addition to morphine which I believe carries distinctly harmful potentialities and that is digitalis. I feel very strongly that digitalis should not be given just because the patient has been laboring for a long time. It should not be given unless there is definite demonstrable evidence of cardiac dilatation or enlargement. Stewart last year reported his observations on digitalization on individuals with enlarged hearts and with normal hearts. The enlarged heart came down to normal and the cardiac output which had been diminished became increased toward normal, but the normal heart, the normal size heart digitalized also became small, smaller than normal, and the cardiac output decreased below normal. So that there is distinct possibility of interfering with circulatory efficiency by digitalizing a heart that is not enlarged.

I had one death which I have been unable to account for otherwise. This individual was an intractable asthmatic who had had her asthma almost constantly for three years. She had had several attacks as severe as her final attack, but in the final attack, her attending physician gave her digitalis to full digitalization, just because she had been having the condition so long he thought probably the heart was weak. She died. We obtained an autopsy. There was nothing in the lungs, nothing in the bronchi. They were clean and almost dry. There were no plugs and the heart was as small a heart as I have ever seen in proportian to the patient's size. It was the only abnormal finding.

Dr. Alexander mentions in his monograph the fact that in even long-standing asthma, you do not as a rule get cardiac dilatation from the asthma.

Dr. Louis Sternberg, New York City.—I have come across patients such as Dr. Clarke discussed. A few were referred for radiothermic treatment, which is an artificial means of raising general body temperature. Six patients who did not respond to other therapeutic measures were given this form of therapy. Only two have responded favorably

so far, and have been free from asthma for over seven months. The temperature of one unimproved case ran up at one occasion to 108 degrees without any ill effects.

DR. J. A. CLARKE, JR.—What I was trying to do was to establish a type of asthma between the acute attack and the chronic state, a type which is of self-limited duration, usually less than a week, which has a definite onset and runs a definite clinical course. It occurs in patients irrespective of whether they are skin-sensitive or not. We have seen a number of instances in typical ragweed sufferers who over a period of years have their trouble entirely limited to the ragweed season.

A great many different suggestions on treatment have been made. This condition is comparatively rare. I do not suppose, even in our busy asthma clinics, we see over a dozen cases that fall into this classification in the course of a year's time, so naturally one does not have a chance to try all the various remedies that are suggested.

Its onset is recognized by increase in dyspnea, the new larger doses of adrenalin and the absence of complete relief after the administration. As soon as we recognized that condition, we put them on five to ten minims of adrenalin hypodermically every hour, whether they need it or not and full doses of potassium iodide to liquefy the sputum. So far that has worked rather well. We have not seen any of these patients die.

As to atelectasis, I read a paper before this Society a number of years ago on atelectasis in asthma and so have kept the condition constantly in mind. I believe it is rare in asthma. We feel that the free administration of morphine predisposes to atelectasis by decreasing the cough reflex, lowering the respiratory rate and lowering the respiratory excursion. One patient I saw at Blockley was breathing four times to the minute. He had been given morphine in large and frequent doses because adrenalin had no effect. Naturally, he only lasted a few hours after I saw him in that condition.

Obstructive emphysema, on the other hand, I think, is very often a factor. The difference in diagnosis between emphysema and atelectasis is, in the first place, the absence of x-ray findings and of cardiac or trachea displacement in the former. There is diminution in breath sounds over the involved area in both conditions. Obstructive emphysema, we believe, not infrequently goes on to pneumonia. Most of the cases of pneumonia we have seen we feel sure started as obstructive emphysema and not as atelectasis.

I do not agree with Dr. Vaughan on digitalis. The heart usually holds up remarkably well in these patients. However, we do not give digitalis routinely. We wait until extrasystoles appear or other signs

of cardiac failure, and then we digitalize rather freely, using a dram of the tincture each four or five hours for a couple of days.

The Relation of Papular Urticaria and Prurigo Mitis to Allergy.

ABRAHAM WALZER AND MAX GROLNICK, Brooklyn, N. Y. (Abstract.)

The writers investigated a series of 40 children (under eleven years), of whom 36 had papular urticaria, and 4 had prurigo mitis. An effort was made to determine the rôle of hypersensitiveness in the etiology of these diseases. All patients were tested intracutaneously by the direct method of Cooke, and in addition, thirteen papular urticarias and three prurigos were tested by the indirect method of Walzer.

An analysis of the findings yields the following facts:

1. Seventeen (47 per cent) of the papular urticaria patients, and all four prurigos gave positive allergic family histories; six of the former gave past or present personal histories of allergies, as eczema or asthma.

2. Positive skin tests to one or more antigens were only obtained in nine patients with papular urticaria (25 per cent of the entire series), and all of these were in the group with positive family histories of allergy. Among these were found the six patients with past or present personal allergies. The positive skin tests seemed related to these associated personal allergies, and not to the papular urticaria or prurigo.

3. A high increase in eosinophiles was usually found to be associated with a positive family history or positive personal history of allergy, and with positive skin tests. A count of 3.8 per cent seemed to be the average for the simple uncomplicated case of papular urticaria.

4. Specific therapy, as indicated by the skin tests, or nonspecific therapy, was of no benefit in the treatment of these conditions.

It seems probable that papular urticaria is an atopic disease, but it is not mediated by the same mechanism as those associated with positive cutaneous (reaginic) reactions, such as asthma, hay fever, and eczema. The same is also probably true of prurigo mitis. Positive skin tests obtained in patients with these diseases bear no relation to the papular urticaria or prurigo, but to sensitivities associated with other reaginic atopic illnesses, past, present, or future. Skin testing in papular urticaria therefore is of no diagnostic value.

DISCUSSION

DR. MATTHEW WALZER.—I wish to bring out something in connection with this paper which may also apply to some of the other papers we have heard today. We have here an instance of positive skin reactions which ordinarily would be considered of diagnostic importance, particularly so because we were able to transfer them by the indirect method

of testing. The impression is gaining ground among those doing this type of work that if we can demonstrate passive transfer, we have something which is absolutely definite as far as an etiologic factor is concerned. That is a dangerous conclusion to draw. Reagins are not pathognomonic of atopy. We find reagins for intestinal parasites in nonatopic individuals. Those infested with hookworm, trichophyton, and so on, have reagins which are definitely demonstrable by passive transfer. Yet these do not indicate any atopic sensitivity in the ordinary individual.

We find reagins demonstrated time and again during the course of serum disease. They also are of no clinical significance as far as we are able to show. It may well be that reagins can be demonstrated in normal individuals following the use of tobacco, and this possibly may have something to do with the reactions demonstrated today by Dr. Harkavy. In that relation, I would like to call attention to the fact that we test our children by the indirect method routinely with tobacco and we have been surprised to find in youngsters, under two years of age, definite transfers of tobacco hypersensitiveness. What this means, I am not ready to state. It is obvious, however, that one must not be too hasty in trying to draw a conclusion as to the etiology, the specific cause or mechanism of an illness merely because he can demonstrate reagins in the patient.

Popular urticaria is another one of those illnesses in which we can get positive transfers with reagins, but caution is needed in interpreting their significance. We have come to the conclusion that these reagins, even though they are present, are not the mechanism of papular urticaria.

Dr. M. B. Sulzberger, New York City.—The disease which is called papular urticaria and the disease which is called prurigo mitis, each enjoys the rather dubious advantage of having about one hundred names which are synonymous. If I could remember them all, I could spend the rest of the time of my discussion rattling them off. In my opinion, these diseases may be transitional phases from some forms of ordinary urticarias to the disseminated neurodermites. At any rate, all dermatologists agree that this group is essentially similar to the neurodermites upon which Drs. Spain, Shahon, Sammis and I reported at the meeting of this Society last year. It is gratifying to find that the results of Dr. Walzer's and Dr. Grolnick's investigations are identical with ours so far as concerns the finding of atopic histories, the association with other atopic diseases, the positive skin tests and the finding of reagins.

In regard to the question of what these positive skin tests and reagins mean, it is proper to ask, as Drs. Walzer and Grolnick have done: did the elimination of the substances giving the positive skin test bring

satisfactory results? We said in our paper that such elimination was a useful *adjuvant* to the therapy. There is no doubt that by getting a neurodermite case reasonably well, relatively free of skin eruption, we could cause an exacerbation of the skin symptoms (in some cases) by administering the correct one of the substances to which the patient had positive skin tests and to which it had been proved he had reagins. However, I think a great many of the positive skin tests and the positive reagin findings must be classed as accompanying polyvalent reactions, perhaps with no clinical significance. This should not astonish us, for we find the same phenomenon in other atopic and allergic diseases; for instance, in a ragweed case, i.e., a case which is clinically and seasonally a ragweed hay fever and gives a ragweed reaction and has ragweed reagins, one will frequently find positive skin tests and reagins to other substances which seem to have no clinical significance. What these mean is not exactly clear in these cases either.

A good example of the clinical significance of some of the positive tests is found in our cases of adults with neurodermatitis, with positive reactions to silk and silk reagins. Many of these cases have never had silk asthma, or rhinitis, or any other atopic disease (some were thirty to forty years old). It is obviously illogical to say the skin test of unknown clinical meaning is related rather to the underlying atopy or to an asthma which never came, rather than to the actual skin disease. In some of these cases I could produce symptoms by letting the patient wear silk. Many of these patients knew they felt better and were more free of their skin trouble when they avoided contact with silk. The same thing was true in a case of neurodermite with fish reagins and immediate wheal reaction to fish. We could cause the symptoms to appear in the skin by letting the patient eat fish, and she herself knew that her skin got worse when she ate fish. So while many of these positive reactions are not in direct relationship to the clinical picture, and I agree absolutely with Dr. Walzer that thus far the elimination of the substances which give the reaction is not of great benefit therapeutically, still some of the substances giving reactions seem to play a rôle in the causation of the skin disease.

I think we will probably get much further if we follow what I said this morning and realize that many of our cases and those of Drs. Walzer and Grolnick were sensitive not only to foods, but also to inhalants. Therefore, in addition to eliminating foods by diet, we must eliminate all the suspected inhalants. This is practically impossible today, but we are working toward this goal. Until we have achieved this complete elimination, I do not believe that we can say which skin tests are of significance in the clinical picture and in the treatment of papular urticaria, prurigo mitis and disseminated neurodermites.

I have always stressed the fact that a positive skin test is of significance *only in corroboration of clinical evidence incriminating the substance eliciting the skin reaction.* In hay fevers, the seasonal nature of the disease shows us that in a patient having, let us say, positive skin tests and reagins to ragweed, egg and horsehair, the ragweed test is the one of clinical significance. In neurodermites, papular urticarias and prurigo mitis we are, unfortunately, almost always without a similar clinical guide to point out which of the many positive reactions are significant. We must, therefore, eliminate both foods and inhalants; i.e., *all* substances giving reactions. Then, when and if the skin improves, see which substance causes an exacerbation. To accomplish this we allow renewed contact with the suspects, carefully and one by one. This is an ideal, far from being practicable now, but until we have done this, at least experimentally in a series of cases, we cannot, in my opinion, say that all our positive tests are of no significance in these skin diseases.

Dr. Robert Chobot, New York City.—I am very much interested in Dr. Walzer's paper and I am exceedingly interested in Dr. Sulzburger's discussion. I would like to cast my vote whole-heartedly and very emphatically in favor of the paper that was read. We have been working on children that have urticaria and, briefly, the results are dubious. The skin reactions in these cases mean absolutely nothing. You can take your positive skin test, take the offending food and feed it to the child and nothing happens. That happens so uniformly that I think it is about time the Society more or less puts itself on record in relationship to our beliefs and understandings of urticaria—well, more clearly than we have in the past.

I think Dr. Cooke believes, as I do, that the urticarias that appear immediately on the ingestion of a food, irrespective of whether papular urticaria or the angioneurotic type, in those cases the skin reactions and the reagins you demonstrate have a real meaning. In the cases where there is not the history of the ingestion of the food followed by the clear demonstration of hives of whatever type they made be, those cases the fetish of skin testing is absolutely worthless, and has been overrated and I think is casting a shadow of ill repute over the field of allergy in many cases.

Dr. A. Walzer.—Our series of cases ranged in age from a few months to eleven years. Dr. Sulzburger's references of neurodermatitis applied to practically all cases of adults.

This whole question of papular urticarias, prurigo, and neurodermatitis, is in a very much disrupted and unstable state. Papular urticaria, to my mind, is an entity, and I do not think it ever leads to neurodermatitis. Once it has been established, it is just as clear-cut and dif-

ferent as asthma is from hay fever. Neurodermatitis once it has been established, is clear-cut and definite and has no relation and no connection, at least clinically, with the papular urticaria or prurigo mitis. I therefore think we are justified in grouping these cases separately until we know more about them.

As to the question of treatment of these patients by the elimination of substances giving positive tests, we have said that in spite of that, no relief or cure was noted in the papular urticarias or the prurigo. In the neurodermatitis, I think Dr. Sulzburger is probably correct, in that there are certain types of those cases in which one can probably aggravate the condition or improve it by the elimination of the positive reacting substances. In the urticarias of children we have found such procedure of no value. Every child with an urticaria that appears before a pediatrician is placed upon a diet, which is juggled in every direction, and apparently without any result. I think that our experiments here show that these conditions, if they are allergic, are probably allergic in a different sense and on a different mechanism than that which we can demonstrate by the tests.

Atopic and Bacterial Asthmatics. M. B. COHEN, Cleveland, Ohio. (For original article, see page 367.)

DISCUSSION

DR. FRANCIS M. RACKEMANN, Boston.—We also have been interested in the responses of atopic and normal individuals to histamine. We have studied the size of the skin tests which result when histamine of different dilutions is injected by the intracutaneous method, and, we also find a difference between the two groups. But the difference is small. The normal person reacts to a dilution of 1:100,000 and the asthmatics react to this same dilution, but on the whole the asthmatics will give larger wheals than normal persons will give.

DR. M. B. SULZBURGER, New York City.—I was talking to Dr. Cohen about his results at luncheon and I mentioned two papers with which he is acquainted. They are by W. Jadassohn,* who reported the following experiments: He injected primary whealing substances in normal individuals and excised the wheal after thirty minutes and at seven hours. Jadassohn also injected the proper excitant in passively sensitized sites in normal individuals and thirty minutes and seven hours later did biopsies and histologic examination of these. He reports that he could find no definite or constant differences in the wheals. That is, the morphine, pilocarpine and atropine wheals, which were surely not due to allergy, were of the same nature and had the same

*Arch. f. Dermat. & Syph. **166**: 458, 1932, and ibid. **167**: 704, 1933.

degree of inflammatory response as the passive-transference site wheal in a passively sensitized individual.

Dr. Cohen's work and Jadassohn's are not comparative; the differences may be due to the fact that in Jadassohn's experiments a normal individual was used, and in Dr. Cohen's a person suffering from a nonatopic type of asthma. Furthermore the biopsies were performed at different times.

I am mentioning this work mainly to point out that in the wheals caused in normal individuals by injections of primary whealing substances such as histamine, morphine, codeine, atropine, etc., there are great numbers of *eosinophiles* (both vascular and extravascular *eosinophiles*). The eosinophilic cells are found in these *surely nonallergic* wheals in as great numbers as are found in the wheals caused by the excitant in the sensitive or passive by sensitized skin. *Therefore, one can no longer regard the presence of eosinophiles (at least in a skin reaction) as in any way indicative of an antigen-antibody reaction, or of allergy or of atopy.*

Dr. Salvatore J. Parlato, Buffalo, N. Y.—I think Dr. Cohen's paper is not only interesting but of value because it has helped to focus our attention upon the problem of variations of skin reactions. After hearing what Dr. Walzer said about the value of skin tests in the diagnosis of skin conditions, it seems that we almost have to start all over again in looking for some diagnostic procedure. However, Dr. Cohen's work may help a great deal to understand the mechanism of some of these skin reactions which we now interpret as nonspecific.

Also, if we can work out some procedure in which we can study more definitely the difference between histamine reactions and the true atopic reactions of the skin, we can distinguish more readily between the so-called atopic and the nonatopic allergic patients.

Dr. Cohen.—If I may have the privilege of erasing some lines on the board, I will try to explain some things which I did not put in my paper because they have been previously published; and also to explain the apparent difference between some of our observations and those of Jadassohn.

We have removed these specimens from five minutes to twenty-two hours after injection so that we have had, not in the same patient, but in a series of patients, opportunity to observe these things at different times although in some patients we have had five or six specimens removed five or ten minutes apart—at five- or ten-minute intervals. After you get that many pieces out of the abdominal wall, the patient doesn't want to have any more out, so you cannot do this thing consecutively in any one patient.

Chart 1 shows the relative severity of the histamine reaction in atopic and nonatopic individuals, compared with the reaction produced by allergen. The histamine reaction in the nonatopic is minimal, but in the atopic it is practically indistinguishable from the specific atopen reactions. Dr. Kline says that if you give him both specimens he can

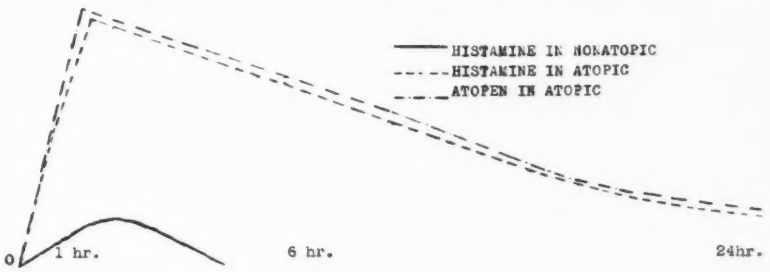

Chart 1.

tell the atopen from the histamine as it is somewhat more marked. To put it in army parlance, histamine in the atopic individual ranks with but after atopen.

As shown in Chart 2 these reactions can be differentiated from ordinary inflammatory reactions only in the first hour or two, since it is

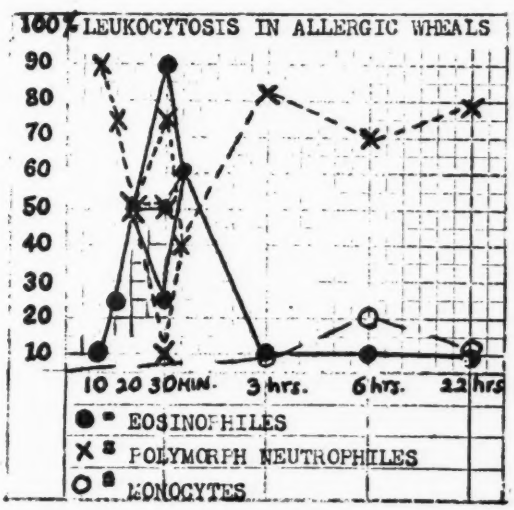

Chart 2.

during this time that the characteristic eosinophilia occurs. Later the neutrophiles and mononuclear cells of ordinary inflammation are seen.

DR. RACKEMANN.—Will you put in the average time reactions?

DR. COHEN.—This will be sixty minutes, this twenty-four hours.

DR. ALEXANDER.—That does not correspond with the disappearance of the wheals.

DR. COHEN.—Oh, no, many of these reactions are gone in an hour so far as the whealing. These are not surface phenomena. We have not measured or made any attempt to find out by dilutions of histamine whether there is more or less reaction. We tried to use a concentration of histamine which in an atopic individual would give us a reaction comparable to the ragweed. We found, for instance, with codeine that the codeine solution has to be more dilute in relation to its concentration than histamine in order to get a comparable reaction. We tried first 1 to 30 codeine and we got very marked reactions, finally we got about 1 to 300 codeine which corresponded to our 1 to 100 histamine.

DR. SULZBURGER.—Did you find eosinophiles in the histamine reaction in the nonatopic individual?

DR. COHEN.—Yes, but very few cells of any kind. The reactions are minimal. At about this point, you reach the maximum, then it tapers off so if you submitted them to almost any histologist, he would pass them by and say there is practically nothing wrong with this section of skin. You have to look fairly closely to see anything wrong.

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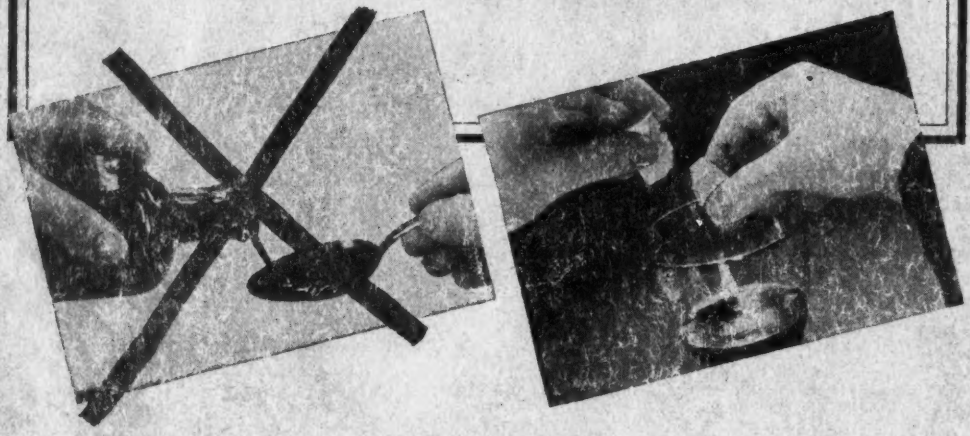

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